COMUNE DI SESTINO

Provincia di Arezzo

Ufficio del Sindaco

DESTINAZIONE:

Ministero dell'Ambiente e della Sicurezza Energetica
Direzione Generale Valutazioni Ambientali
Via Cristoforo Colombo 44 - 00147 Roma (Italia)
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Oggetto:

Procedimenti di VIA statale PNIEC, Progetti di Parchi Eolici denominati "Poggio delle Campane", "Sestino" e "Energia Monte Petralta" ubicati nel Comune di Badia Tedalda (AR) e nel Comune di Sestino (AR), costituiti da aerogeneratori, con relative opere connesse ed infrastrutture nel Comune di Sestino – *PARERE DEL COMUNE DI SESTINO – DELIBERA DI GIUNTA MUNICIPALE N. 35/2024 del 29 MARZO 2024*.

Premesso che sono pervenuti dal Ministero dell'Ambiente e della Sicurezza Energetica (MASE) per l'avvio di un procedimento di Valutazione di Impatto Ambientale (VIA) di competenza statale per progetti relativi alla Valutazione di Impatto Ambientale ai sensi del D.Lgs n. 152/02 per la realizzazione di Parchi Eolici denominati *"Poggio delle Campane", "Sestino"* e *"Energia Monte Petralta*" tutti insistenti nel territorio comunale di Sestino (AR).

Esulando ovviamente dagli obbligatori pareri tecnico-gestionali d'ufficio, che restano di competenza esclusiva e professionale del Ufficio Tecnico Comunale delo scrivente Ente, la Giunta Municipale del Comune di Sestino è stata dunque chiamata, necessariamente, ad esprimere una propria valutazione sulla progettualità in oggetto, analizzando altresi' elementi e caratteri antropologici e naturalistico-territoriali.

E' stato effettuato uno studio attento e concreto della progettualità in trattazione, analizzando una pluralità di aspetti, e ponendo sulla bilancia gli elementi positivi e quelli negativi.

Il Comune di Sestino ha voluto coinvolgere anche la popolazione, e chiari sono i documenti (alcuni dei quali allegati alla presente….) e le sottoscrizioni (che continuano a giungere ai ns. uffici) nelle quali i nostri Cittadini hanno espresso un deciso parere contrario ai progetti dei Parchi Eolici.

E' giusto osservare che i progetti dei Parchi Eolici in trattazione andrebbero a realizzarsi, materialmente, nelle cd. "aree interne" dell'Appennino, con un ambiente ancora incontaminato e splendidamente variegato per i suoi contenuti naturalistici. Si tratta di territori complessi, ove in questi ultimi anni, anche allo scopo di ridurre una costante tendenza allo spopolamento, sono stati fatti dei buoni investimenti, per favorire il turismo e la conservazione delle tradizioni culturali locali.

In particolare, per quanto riguarda il nostro Comune, i Parchi Eolici andrebbero ad essere collocati in un ambito caratterizzato da ricchezze naturalistico-culturali quali i "Sentieri di Francesco", le ciclopiste, la sentieristica del CAI, il "Sentiero del Granduca" e altri "tesori".

Non meno importante la possibile incidenza sulle attività produttive tipiche dei nostri territori, come gli allevamenti di Chianine, le zone tartufigene…. e non ultimi i diversi B&B, che sono sorti in questo ultimo periodo come nuovo elemento di attrazione per gli stranieri e per le famiglie che "fuggono" dalle città per cercare momenti di pace e di tranquillita'.

E chiaramente non puo' essere dimenticato che il progetto eolico in questione andrebbe a svilupparsi, materialmente e "spiritualmente", attorno alla Riserva Naturale del Sasso di Simone, dal confine valmarecchiese con Miratoio ai crinali del Seminico, per continuare sulle alture di Monteromano, Martigliano e al confine con il Parco Interregionale di Carpegna, con tutte le conseguenze che possono facilmente essere intuite, incidendo inevitabilmente sulla biodiversità tipica dell'area protetta .

Purtroppo…..ed è cosa piuttosto nota…. e importanti studi scientifici lo confermano, gli "insediamenti" di pale eoliche, che nel nostro caso avrebbero anche la caratteristica di essere "mega", sconsigliano di vivere nelle loro vicinanze, trasformano la fauna, e spesso anche la flora, per cause di interconnessione tra microclima, vegetazione e suolo prativo.

Alcune delle nostre piu' belle località frazionali, come Petrella, Case Barboni, Martigliano, Casale, San Donato, Monterone, Colcellalto sarebbero le prime a soffrire di un ambiente artefatto, anche rumoroso, e perciò invivibile.

Verrebbero colpite le attività di allevamento della RAZZA CHIANINA allo stato brado e semibrado, mentre i nuovi flussi turistici naturalistici, ad oggi faticosamente conquistati, ne risentirebbero immediatamente e la conseguenza sarebbe un nuovo definitivo spopolamento dei territori interessati.

D'altro canto non sara' inutile segnalare che già molte associazioni, semplici Cittadini, "comitati" hanno voluto dare il loro contributo, relazionando pareri fortemente negativi nei confronti della progettualità eolica, e fra gli altri ricordiamo le osservazioni del Club Alpino Italiano, le osservazioni dell'Associazione Mountain Wilderness Italia, le osservazioni dell'Associazione Italia Nostra, le osservazioni del Comitato Appennino Sostenibile, le osservazioni dell'Associazione Altura e quelle del CAI GRUPPO REGIONALE TOSCANA.

Per tutte le motivazioni di cui sopra, la Giunta Municipale di questo Ente ha adottato l'allegato atto deliberativo (Deliberazione di GIUNTA MUNICIPALE n. 35/2024), esprimendo una chiaro parere negativo e contrario allo sviluppo realizzativo dei Progetti di Impianti Eolici denominati *"Poggio delle Campane", "Sestino"* e "*Energia Monte Petralta"* ubicati nel Comune di Sestino (AR), con relative opere connesse ed infrastrutture .

Nel ribadire dunque la posizione del Comune di Sestino in merito alla progettualità in trattazione, si invia la presente nota, allegando in copia la succitata Deliberazione G.M. n. 35/2024 (e relativi allegati di riferimento), sottolineando che in questi giorni continuano ad arrivare agli uffici comunali altre sottoscrizioni di Cittadini fortemente contrari al progetto eolico in oggetto.

IL SINDACO DEL COMUNE DI SESTINO

DORI FRANCO

Sestino, 09 APRILE 2024
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WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

VOLUME 80
NON-IONIZING RADIATION, PART 1: STATIC AND EXTREMELY LOW-FREQUENCY (ELF) ELECTRIC AND MAGNETIC FIELDS

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F R A N C E

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Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields

VOLUME 80

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

19–26 June 2001

2002

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, life-style factors and biological and physical agents, as well as those in specific occupations.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed.

The lists of IARC evaluations are regularly updated and are available on Internet: http://monographs.iarc.fr/

This project was supported by Cooperative Agreement 5 UO1 CA33193 awarded by the United States National Cancer Institute, Department of Health and Human Services, and was funded in part by the European Commission, Directorate-General EMPL (Employment, and Social Affairs), Health, Safety and Hygiene at Work Unit. Additional support has been provided since 1993 by the United States National Institute of Environmental Health Sciences.

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NOTE TO THE READER

The term ‘carcinogenic risk’ in the *IARC Monographs* series is taken to mean the probability that exposure to an agent will lead to cancer in humans.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Carcinogen Identification and Evaluation, so that corrections can be reported in future volumes.

IARC WORKING GROUP ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: NON-IONIZING RADIATION, PART 1, STATIC AND EXTREMELY LOW-FREQUENCY (ELF) ELECTRIC AND MAGNETIC FIELDS

Lyon, 19–26 June 2001

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PREAMBLE

IARC MONOGRAPHS PROGRAMME ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

PREAMBLE

1. BACKGROUND

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. The *Monographs* programme has since been expanded to include consideration of exposures to complex mixtures of chemicals (which occur, for example, in some occupations and as a result of human habits) and of exposures to other agents, such as radiation and viruses. With Supplement 6 (IARC, 1987a), the title of the series was modified from *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* to *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, in order to reflect the widened scope of the programme.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs series*. Those criteria were subsequently updated by further ad-hoc working groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987b, 1988, 1991a; Vainio *et al.*, 1992).

2. OBJECTIVE AND SCOPE

The objective of the programme is to prepare, with the help of international working groups of experts, and to publish in the form of monographs, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* may also indicate where additional research efforts are needed.

The *Monographs* represent the first step in carcinogenic risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that certain exposures could alter the incidence of cancer in humans. The second step is quantitative risk estimation. Detailed, quantitative evaluations of epidemiological data may be made in the *Monographs*, but without extrapolation beyond the range of the data available. Quantitative extrapolation from experimental data to the human situation is not undertaken.

The term ‘carcinogen’ is used in these monographs to denote an exposure that is capable of increasing the incidence of malignant neoplasms; the induction of benign neoplasms may in some circumstances (see p. 19) contribute to the judgement that the exposure is carcinogenic. The terms ‘neoplasm’ and ‘tumour’ are used interchangeably.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991a; Vainio *et al.*, 1992; see also pp. 25–27).

The *Monographs* may assist national and international authorities in making risk assessments and in formulating decisions concerning any necessary preventive measures. The evaluations of IARC working groups are scientific, qualitative judgements about the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which regulatory measures may be based. Other components of regulatory decisions vary from one situation to another and from country to country, responding to different socioeconomic and national priorities. **Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments and/or other international organizations.**

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of a wide range of human exposures. A survey of users in 1988 indicated that the *Monographs* are consulted by various agencies in 57 countries. About 2500 copies of each volume are printed, for distribution to governments, regulatory bodies and interested scientists. The Monographs are also available from IARC*Press* in Lyon and via the Distribution and Sales Service of the World Health Organization in Geneva.

3. SELECTION OF TOPICS FOR MONOGRAPHS

Topics are selected on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some evidence or suspicion of carcinogenicity. The term ‘agent’ is used to include individual chemical compounds, groups of related chemical compounds, physical agents (such as radiation) and biological factors (such as viruses). Exposures to mixtures of agents may occur in occupational exposures and as a result of personal and cultural habits (like smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. The IARC information bulletins on agents being tested for carcinogenicity (IARC, 1973–1996) and directories of on-going research in cancer epidemiology (IARC, 1976–1996) often indicate exposures that may be scheduled for future meetings. Ad-hoc working groups convened by IARC in 1984, 1989, 1991, 1993 and 1998 gave recommendations as to which agents should be evaluated in the IARC Monographs series (IARC, 1984, 1989, 1991b, 1993, 1998a,b).

As significant new data on subjects on which monographs have already been prepared become available, re-evaluations are made at subsequent meetings, and revised monographs are published.

4. DATA FOR MONOGRAPHS

The *Monographs* do not necessarily cite all the literature concerning the subject of an evaluation. Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to biological and epidemiological data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed by the working groups. In certain instances, government agency reports that have undergone peer review and are widely available are considered. Exceptions may be made on an ad-hoc basis to include unpublished reports that are in their final form and publicly available, if their inclusion is considered pertinent to making a final evaluation (see pp. 25–27). In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, unpublished sources of information may be used.

5. THE WORKING GROUP

Reviews and evaluations are formulated by a working group of experts. The tasks of the group are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanism of action; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans.

Working Group participants who contributed to the considerations and evaluations within a particular volume are listed, with their addresses, at the beginning of each publication. Each participant who is a member of a working group serves as an individual scientist and not as a representative of any organization, government or industry. In addition, nominees of national and international agencies and industrial associations may be invited as observers.

6. WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, the topics of the monographs are announced and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by the Carcinogen Identification and Evaluation Unit of IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as MEDLINE and TOXLINE.

For chemicals and some complex mixtures, the major collection of data and the preparation of first drafts of the sections on chemical and physical properties, on analysis,

on production and use and on occurrence are carried out under a separate contract funded by the United States National Cancer Institute. Representatives from industrial associations may assist in the preparation of sections on production and use. Information on production and trade is obtained from governmental and trade publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available because their publication could disclose confidential information. Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants, or is used by IARC staff, to prepare sections for the first drafts of monographs. The first drafts are compiled by IARC staff and sent before the meeting to all participants of the Working Group for review.

The Working Group meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, edited and prepared for publication. The aim is to publish monographs within six months of the Working Group meeting.

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study, directly impinging on its interpretation, should be brought to the attention of the reader, a comment is given in square brackets.

7. EXPOSURE DATA

Sections that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are included at the beginning of each monograph.

Most monographs on individual chemicals, groups of chemicals or complex mixtures include sections on chemical and physical data, on analysis, on production and use and on occurrence. In monographs on, for example, physical agents, occupational exposures and cultural habits, other sections may be included, such as: historical perspectives, description of an industry or habit, chemistry of the complex mixture or taxonomy. Monographs on biological agents have sections on structure and biology, methods of detection, epidemiology of infection and clinical disease other than cancer.

For chemical exposures, the Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name and the IUPAC Systematic Name are recorded; other synonyms are given, but the list is not necessarily comprehensive. For biological agents,

taxonomy and structure are described, and the degree of variability is given, when applicable.

Information on chemical and physical properties and, in particular, data relevant to identification, occurrence and biological activity are included. For biological agents, mode of replication, life cycle, target cells, persistence and latency and host response are given. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

The purpose of the section on analysis or detection is to give the reader an overview of current methods, with emphasis on those widely used for regulatory purposes. Methods for monitoring human exposure are also given, when available. No critical evaluation or recommendation of any of the methods is meant or implied. The IARC published a series of volumes, *Environmental Carcinogens: Methods of Analysis and Exposure Measurement* (IARC, 1978–93), that describe validated methods for analysing a wide variety of chemicals and mixtures. For biological agents, methods of detection and exposure assessment are described, including their sensitivity, specificity and reproducibility.

The dates of first synthesis and of first commercial production of a chemical or mixture are provided; for agents which do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided. In addition, methods of synthesis used in past and present commercial production and different methods of production which may give rise to different impurities are described.

Data on production, international trade and uses are obtained for representative regions, which usually include Europe, Japan and the United States of America. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice, nor does it imply judgement as to their therapeutic efficacy.

Information on the occurrence of an agent or mixture in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. In the case of mixtures, industries, occupations or processes, information is given about all agents present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with time and place. For biological agents, the epidemiology of infection is described.

Statements concerning regulations and guidelines (e.g., pesticide registrations, maximal levels permitted in foods, occupational exposure limits) are included for some countries as indications of potential exposures, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccines and therapy, are described.

8. STUDIES OF CANCER IN HUMANS

(*a*) *Types of studies considered*

Three types of epidemiological studies of cancer contribute to the assessment of carcinogenicity in humans—cohort studies, case–control studies and correlation (or ecological) studies. Rarely, results from randomized trials may be available. Case series and case reports of cancer in humans may also be reviewed.

Cohort and case–control studies relate the exposures under study to the occurrence of cancer in individuals and provide an estimate of relative risk (ratio of incidence or mortality in those exposed to incidence or mortality in those not exposed) as the main measure of association.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent, mixture or exposure circumstance under study. Because individual exposure is not documented, however, a causal relationship is less easy to infer from correlation studies than from cohort and case–control studies. Case reports generally arise from a suspicion, based on clinical experience, that the concurrence of two events—that is, a particular exposure and occurrence of a cancer—has happened rather more frequently than would be expected by chance. Case reports usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure. The uncertainties surrounding interpretation of case reports and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, relevant case reports or correlation studies may add materially to the judgement that a causal relationship is present.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed by working groups. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(*b*) *Quality of studies considered*

The Monographs are not intended to summarize all published studies. Those that are judged to be inadequate or irrelevant to the evaluation are generally omitted. They may be mentioned briefly, particularly when the information is considered to be a useful supplement to that in other reports or when they provide the only data available. Their

inclusion does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of the study description.

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. By 'bias' is meant the operation of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between disease and an agent, mixture or exposure circumstance. By 'confounding' is meant a situation in which the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. In evaluating the extent to which these factors have been minimized in an individual study, working groups consider a number of aspects of design and analysis as described in the report of the study. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken account in the study design and analysis of other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may be more appropriate than those with national rates. Internal comparisons of disease frequency among individuals at different levels of exposure should also have been made in the study.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. The methods used should preferably have been the generally accepted techniques that have been refined since the mid-1970s. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(*c*) *Inferences about mechanism of action*

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure and time since exposure ceased, are reviewed and summarized when available. The analysis of temporal relationships can be useful in formulating models of carcinogenesis. In particular, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although at best they allow only indirect inferences about the mechanism of action. Special attention is given to measurements of biological markers of carcinogen exposure or action, such as DNA or protein adducts, as well as markers of early steps in the carcinogenic process, such as proto-oncogene mutation, when these are incorporated into epidemiological studies focused on cancer incidence or mortality. Such measurements may allow inferences to be made about putative mechanisms of action (IARC, 1991a; Vainio *et al.*, 1992).

(*d*) *Criteria for causality*

After the individual epidemiological studies of cancer have been summarized and the quality assessed, a judgement is made concerning the strength of evidence that the agent, mixture or exposure circumstance in question is carcinogenic for humans. In making its judgement, the Working Group considers several criteria for causality. A strong association (a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that relative risks of small magnitude do not imply lack of causality and may be important if the disease is common. Associations that are replicated in several studies of the same design or using different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in amount of exposure), and results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound. When suspicion of carcinogenicity arises largely from a single study, these data are not combined with those from later studies in any subsequent reassessment of the strength of the evidence.

If the risk of the disease in question increases with the amount of exposure, this is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship. Demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Although a carcinogen may act upon more than one target, the specificity of an association (an increased occurrence of cancer at one anatomical site or of one morphological type) adds plausibility to a causal relationship, particularly when excess cancer occurrence is limited to one morphological type within the same organ.

Although rarely available, results from randomized trials showing different rates among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, the judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first of all that the studies giving rise to it meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should be consistent with a relative risk of unity for any observed level of exposure and, when considered together, should provide a pooled estimate of relative risk which is at or near unity and has a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency for the relative risk of cancer to increase with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained in this way from several epidemiological studies can apply only to the type(s) of cancer studied and to dose levels and intervals between first exposure and observation of disease that are the same as or less than those observed in all the studies. Experience with human cancer indicates that, in some cases, the period from first exposure to the development of clinical cancer is seldom less than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

9. STUDIES OF CANCER IN EXPERIMENTAL ANIMALS

All known human carcinogens that have been studied adequately in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (aflatoxins, 4-aminobiphenyl, azathioprine, betel quid with tobacco, bischloromethyl ether and chloromethyl methyl ether (technical grade), chlorambucil, chlornaphazine, ciclosporin, coal-tar pitches, coal-tars, combined oral contraceptives, cyclophosphamide, diethylstilboestrol, melphalan, 8-methoxypsoralen plus ultraviolet A radiation, mustard gas, myleran, 2-naphthylamine, nonsteroidal estrogens, estrogen replacement therapy/steroidal estrogens, solar radiation, thiotepa and vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents and mixtures that cause cancer in experimental animals also cause cancer in humans, nevertheless, **in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is *sufficient evidence* (see p. 24) of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans**. The possibility that a given agent may cause cancer through a species-specific mechanism which does not operate in humans (see p. 27) should also be taken into consideration.

The nature and extent of impurities or contaminants present in the chemical or mixture being evaluated are given when available. Animal strain, sex, numbers per group, age at start of treatment and survival are reported.

Other types of studies summarized include: experiments in which the agent or mixture was administered in conjunction with known carcinogens or factors that modify carcinogenic effects; studies in which the end-point was not cancer but a defined precancerous lesion; and experiments on the carcinogenicity of known metabolites and derivatives.

For experimental studies of mixtures, consideration is given to the possibility of changes in the physicochemical properties of the test substance during collection, storage, extraction, concentration and delivery. Chemical and toxicological interactions of the components of mixtures may result in nonlinear dose–response relationships.

An assessment is made as to the relevance to human exposure of samples tested in experimental animals, which may involve consideration of: (i) physical and chemical characteristics, (ii) constituent substances that indicate the presence of a class of substances, (iii) the results of tests for genetic and related effects, including studies on DNA adduct formation, proto-oncogene mutation and expression and suppressor gene inactivation. The relevance of results obtained, for example, with animal viruses analogous to the virus being evaluated in the monograph must also be considered. They may provide biological and mechanistic information relevant to the understanding of the process of carcinogenesis in humans and may strengthen the plausibility of a conclusion that the biological agent under evaluation is carcinogenic in humans.

(*a*) *Qualitative aspects*

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route and schedule of exposure, species, strain, sex, age, duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

As mentioned earlier (p. 11), the *Monographs* are not intended to summarize all published studies. Those studies in experimental animals that are inadequate (e.g., too short a duration, too few animals, poor survival; see below) or are judged irrelevant to the evaluation are generally omitted. Guidelines for conducting adequate long-term carcinogenicity experiments have been outlined (e.g. Montesano *et al.*, 1986).

Considerations of importance to the Working Group in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was adequately monitored, particularly in inhalation experiments; (iii) whether the doses and duration of treatment were appropriate and whether the survival of treated animals was similar to that of controls; (iv) whether there were adequate numbers of animals per group; (v) whether animals of each sex were used; (vi) whether animals were allocated randomly to groups; (vii) whether the duration of observation was adequate; and (viii) whether the data were adequately reported. If available, recent data on the incidence of specific tumours in historical controls, as

well as in concurrent controls, should be taken into account in the evaluation of tumour response.

When benign tumours occur together with and originate from the same cell type in an organ or tissue as malignant tumours in a particular study and appear to represent a stage in the progression to malignancy, it may be valid to combine them in assessing tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be pre-neoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent or mixture induces only benign neoplasms that appear to be end-points that do not readily progress to malignancy, it should nevertheless be suspected of being a carcinogen and requires further investigation.

(*b*) *Quantitative aspects*

The probability that tumours will occur may depend on the species, sex, strain and age of the animal, the dose of the carcinogen and the route and length of exposure. Evidence of an increased incidence of neoplasms with increased level of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Both DNA damage and increased cell division are important aspects of carcinogenesis, and cell proliferation is a strong determinant of dose–response relationships for some carcinogens (Cohen & Ellwein, 1990). Since many chemicals require metabolic activation before being converted into their reactive intermediates, both metabolic and pharmacokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship, as could saturation of processes such as DNA repair (Hoel *et al.*, 1983; Gart *et al.*, 1986).

(*c*) *Statistical analysis of long-term experiments in animals*

Factors considered by the Working Group include the adequacy of the information given for each treatment group: (i) the number of animals studied and the number examined histologically, (ii) the number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986). When there is no difference in survival between control and treatment groups, the Working Group usually compares the proportions of animals developing each tumour type in each of the groups. Otherwise, consideration is given as to whether or not appropriate adjustments have been made for differences in survival. These adjustments can include: comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour is discovered), in the case where most differences in survival occur before tumours appear; life-table methods, when tumours are visible or when they may be considered ‘fatal’ because mortality rapidly follows tumour development; and the Mantel-Haenszel test or logistic regression,

when occult tumours do not affect the animals' risk of dying but are 'incidental' findings at autopsy.

In practice, classifying tumours as fatal or incidental may be difficult. Several survival-adjusted methods have been developed that do not require this distinction (Gart *et al.*, 1986), although they have not been fully evaluated.

10. OTHER DATA RELEVANT TO AN EVALUATION OF CARCINOGENICITY AND ITS MECHANISMS

In coming to an overall evaluation of carcinogenicity in humans (see pp. 25–27), the Working Group also considers related data. The nature of the information selected for the summary depends on the agent being considered.

For chemicals and complex mixtures of chemicals such as those in some occupational situations or involving cultural habits (e.g. tobacco smoking), the other data considered to be relevant are divided into those on absorption, distribution, metabolism and excretion; toxic effects; reproductive and developmental effects; and genetic and related effects.

Concise information is given on absorption, distribution (including placental transfer) and excretion in both humans and experimental animals. Kinetic factors that may affect the dose–response relationship, such as saturation of uptake, protein binding, metabolic activation, detoxification and DNA repair processes, are mentioned. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data on humans and on animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be of particular importance for extrapolation between species. Data are given on acute and chronic toxic effects (other than cancer), such as organ toxicity, increased cell proliferation, immunotoxicity and endocrine effects. The presence and toxicological significance of cellular receptors is described. Effects on reproduction, teratogenicity, fetotoxicity and embryotoxicity are also summarized briefly.

Tests of genetic and related effects are described in view of the relevance of gene mutation and chromosomal damage to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, where necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests on p. 18. The available data are interpreted critically by phylogenetic group according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations, aneuploidy and cell transformation. The concentrations employed are given, and mention is made of whether use of an exogenous metabolic system *in vitro* affected the test result. These data are given as listings of test systems, data and references. The Genetic and Related Effects data presented in the *Monographs* are also available in the form of Graphic Activity Profiles (GAP) prepared in collaboration with the United States Environmental Protection Agency (EPA) (see also

Waters *et al.*, 1987) using software for personal computers that are Microsoft Windows® compatible. The EPA/IARC GAP software and database may be downloaded free of charge from *www.epa.gov/gapdb*.

Positive results in tests using prokaryotes, lower eukaryotes, plants, insects and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information about the types of genetic effect produced and about the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g., gene mutations and chromosomal aberrations), while others are to a greater or lesser degree associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour-promoting activity and for cell transformation may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. A critical appraisal of these tests has been published (Montesano *et al.*, 1986).

Genetic or other activity manifest in experimental mammals and humans is regarded as being of greater relevance than that in other organisms. The demonstration that an agent or mixture can induce gene and chromosomal mutations in whole mammals indicates that it may have carcinogenic activity, although this activity may not be detectably expressed in any or all species. Relative potency in tests for mutagenicity and related effects is not a reliable indicator of carcinogenic potency. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence to rule out carcinogenicity of agents or mixtures that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative proliferation, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may lead to misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986).

When available, data relevant to mechanisms of carcinogenesis that do not involve structural changes at the level of the gene are also described.

The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is evaluated by the same criteria as are applied to epidemiological studies of cancer.

Structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent are also described.

For biological agents—viruses, bacteria and parasites—other data relevant to carcinogenicity include descriptions of the pathology of infection, molecular biology (integration and expression of viruses, and any genetic alterations seen in human tumours) and other observations, which might include cellular and tissue responses to infection, immune response and the presence of tumour markers.

11. SUMMARY OF DATA REPORTED

In this section, the relevant epidemiological and experimental data are summarized. Only reports, other than in abstract form, that meet the criteria outlined on p. 11 are considered for evaluating carcinogenicity. Inadequate studies are generally not summarized: such studies are usually identified by a square-bracketed comment in the preceding text.

(*a*) *Exposure*

Human exposure to chemicals and complex mixtures is summarized on the basis of elements such as production, use, occurrence in the environment and determinations in human tissues and body fluids. Quantitative data are given when available. Exposure to biological agents is described in terms of transmission and prevalence of infection.

(*b*) *Carcinogenicity in humans*

Results of epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized.

(*c*) *Carcinogenicity in experimental animals*

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species and route of administration, it is stated whether an increased incidence of neoplasms or preneoplastic lesions was observed, and the tumour sites are indicated. If the agent or mixture produced tumours after prenatal exposure or in single-dose experiments, this is also indicated. Negative findings are also summarized. Dose–response and other quantitative data may be given when available.

(*d*) *Other data relevant to an evaluation of carcinogenicity and its mechanisms*

Data on biological effects in humans that are of particular relevance are summarized. These may include toxicological, kinetic and metabolic considerations and evidence of DNA binding, persistence of DNA lesions or genetic damage in exposed humans. Toxicological information, such as that on cytotoxicity and regeneration, receptor binding and hormonal and immunological effects, and data on kinetics and metabolism in experimental animals are given when considered relevant to the possible mechanism of the carcinogenic action of the agent. The results of tests for genetic and related effects are summarized for whole mammals, cultured mammalian cells and nonmammalian systems.

When available, comparisons of such data for humans and for animals, and particularly animals that have developed cancer, are described.

Structure–activity relationships are mentioned when relevant.

For the agent, mixture or exposure circumstance being evaluated, the available data on end-points or other phenomena relevant to mechanisms of carcinogenesis from studies in humans, experimental animals and tissue and cell test systems are summarized within one or more of the following descriptive dimensions:

(i) Evidence of genotoxicity (structural changes at the level of the gene): for example, structure–activity considerations, adduct formation, mutagenicity (effect on specific genes), chromosomal mutation/aneuploidy

(ii) Evidence of effects on the expression of relevant genes (functional changes at the intracellular level): for example, alterations to the structure or quantity of the product of a proto-oncogene or tumour-suppressor gene, alterations to metabolic activation/inactivation/DNA repair

(iii) Evidence of relevant effects on cell behaviour (morphological or behavioural changes at the cellular or tissue level): for example, induction of mitogenesis, compensatory cell proliferation, preneoplasia and hyperplasia, survival of premalignant or malignant cells (immortalization, immunosuppression), effects on metastatic potential

(iv) Evidence from dose and time relationships of carcinogenic effects and interactions between agents: for example, early/late stage, as inferred from epidemiological studies; initiation/promotion/progression/malignant conversion, as defined in animal carcinogenicity experiments; toxicokinetics

These dimensions are not mutually exclusive, and an agent may fall within more than one of them. Thus, for example, the action of an agent on the expression of relevant genes could be summarized under both the first and second dimensions, even if it were known with reasonable certainty that those effects resulted from genotoxicity.

12. EVALUATION

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent, mixture or exposure circumstance to a higher or lower category than a strict interpretation of these criteria would indicate.

(*a*) *Degrees of evidence for carcinogenicity in humans and in experimental animals and supporting evidence*

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency) nor to the mechanisms involved. A classification may change as new information becomes available.

An evaluation of degree of evidence, whether for a single agent or a mixture, is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of degree of evidence.

(i) *Carcinogenicity in humans*

The applicability of an evaluation of the carcinogenicity of a mixture, process, occupation or industry on the basis of evidence from epidemiological studies depends on the

variability over time and place of the mixtures, processes, occupations and industries. The Working Group seeks to identify the specific exposure, process or activity which is considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, conditions and levels of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

(ii) *Carcinogenicity in experimental animals*

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent or mixture is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and levels of exposure studied.

(*b*) *Other data relevant to the evaluation of carcinogenicity and its mechanisms*

Other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is then described. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and pharmacokinetics, physicochemical parameters and analogous biological agents.

Data relevant to mechanisms of the carcinogenic action are also evaluated. The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is assessed, using terms such as weak, moderate or strong. Then, the Working Group assesses if that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans come from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(*c*) *Overall evaluation*

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity to humans of an agent, mixture or circumstance of exposure.

An evaluation may be made for a group of chemical compounds that have been evaluated by the Working Group. In addition, when supporting data indicate that other, related compounds for which there is no direct evidence of capacity to induce cancer in humans or in animals may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of compounds if the strength of the evidence warrants it.

The agent, mixture or exposure circumstance is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent, mixture or exposure circumstance is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1 —The agent (mixture) is carcinogenic to humans.
The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Group 2

This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

Group 2A—The agent (mixture) is probably carcinogenic to humans.
The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans, *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

Group 2B—The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3—The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents, mixtures and exposure circumstances for which the *evidence of carcinogenicity* is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents (mixtures) for which the *evidence of carcinogenicity* is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4—The agent (mixture) is probably not carcinogenic to humans.

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

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GENERAL INTRODUCTION

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1. Introduction

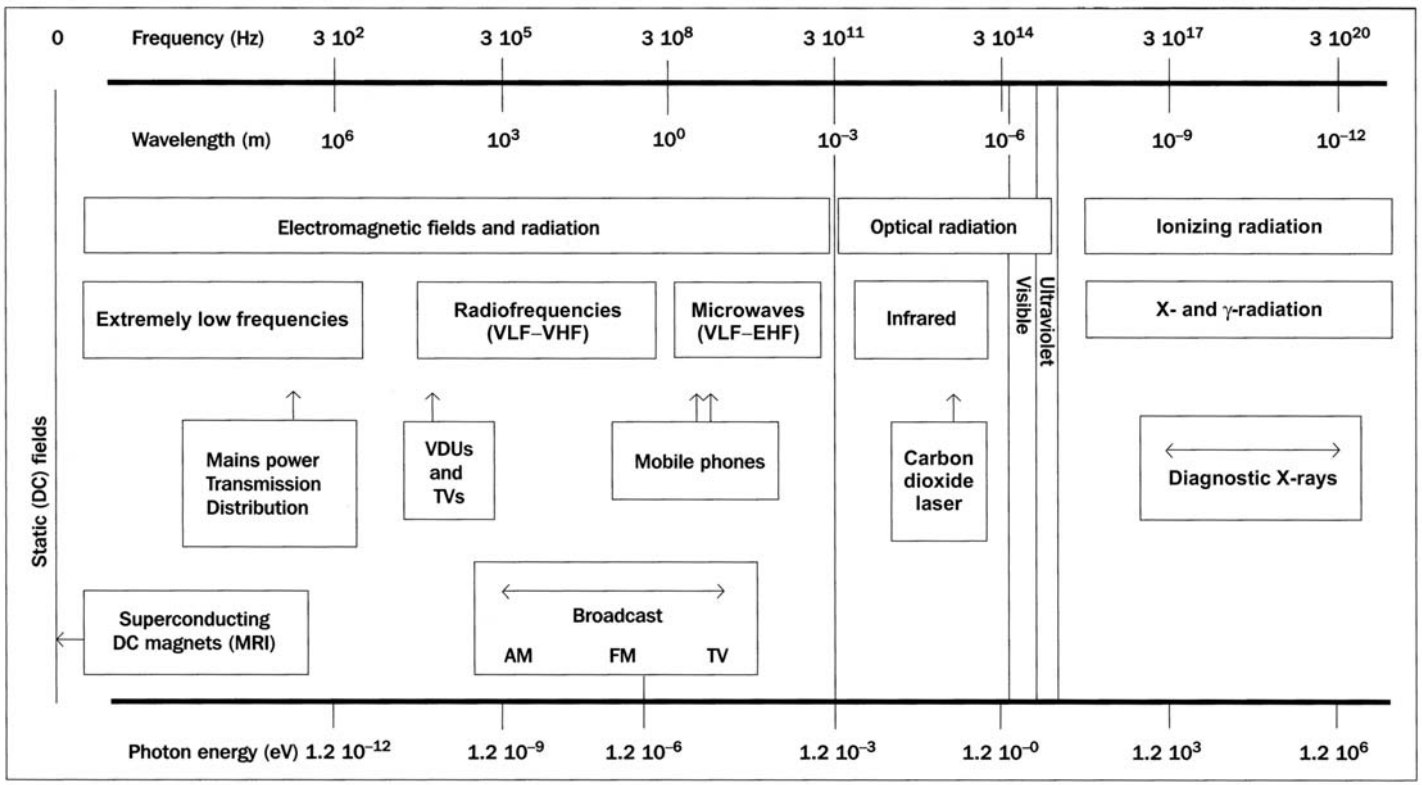
Previous *Monographs* have considered distinct types of electromagnetic radiation: solar and ultraviolet radiation (IARC, 1992) and X- and γ-radiation (IARC, 2000). This volume is concerned with that region of the spectrum described as static and 'extremely low frequency' (ELF). Such electromagnetic energy occurs naturally or in association with the generation and transmission of electrical power and with the use of power in some appliances. It is different from electromagnetic fields and radiation consequent upon the transmission of radio and television signals and the operation of mobile phones (Figure 1).

Static electric and magnetic fields, as well as low-frequency fields, are produced by both natural and man-made sources. The natural fields are static or very slowly varying. The electric field in the air above the earth's surface is typically 100 V/m but during strong electric storms may increase 10-fold or more. The geomagnetic field is typically 50 μT (König *et al.*, 1981). Most man-made sources are at extremely low frequencies. The generation, transmission, distribution and use of electricity at 50 or 60 Hz result in widespread exposure of humans to ELF fields of the order of 10–100 V/m and 0.1–1 μT, and occasionally to much stronger fields (National Research Council, 1997; Portier & Wolfe, 1998; National Radiological Protection Board, 2001). Electrical power is an integral part of modern civilization. Because ELF fields can interact with biological systems, interest and concern about potential hazards are understandable.

The study of the effects of electric and magnetic fields on humans has a long history. Data pertaining to human health risks were first gathered in the 1960s from studies of workers with occupational exposure to ELF fields. The first data to address potential carcinogenic risks were obtained in a series of studies of adults and children with residential exposures from electrical facilities, appliances and external and internal wiring and grounding systems.

Experimental studies have expended considerable effort in the search for mechanism(s) that would predict the biological effects of the low-intensity fields that are found in residential and occupational environments. More recent investigations have focused on obtaining data to assess potential carcinogenic risks. Of particular importance are chronic bioassays that look for microscopic evidence of lesions and

Figure 1. Electromagnetic spectrum



From National Radiological Protection Board (2001)

AM, amplitude modulation; DC, direct current; EHF, extremely high frequency; eV, electron volt; FM, frequency modulation; MRI, magnetic resonance imaging; TV, television; UHF, ultra high frequency; VDU, visual display unit; VHF, very high frequency; VLF, very low frequency

tumours in rodents exposed over most of their lifespan. The default assumption is that the photon energies of ELF fields, as for other forms of non-ionizing radiation, are insufficient to ionize molecules or break chemical bonds in biological systems.

The genotoxicity of electric and magnetic fields has been tested both *in vivo* and *in vitro*. The possibility that these fields may be carcinogenic has been investigated in standard tumour promotion/co-promotion systems. These involve the exposure of rodents to ELF electric and magnetic fields following, or coincident with, the initiation of skin, liver and mammary tumours by chemical initiators.

In addition to a general assessment of the data and mechanisms of toxicity, the characterization of associations between exposure to ELF magnetic fields and cancer, particularly leukaemias and brain tumours, requires focused evaluations of experimental data regarding field effects on haematopoietic cells (leukaemia), the nervous system (brain tumours) and its function and neuroendocrine and immunological factors that might be suspected of influencing susceptibility to cancer.

2. Physical characteristics of electromagnetic fields

The main focus of this *Monographs* volume is on static and time-varying fields in the ELF range of 3–3000 Hz (IEEE, 1988). Ancillary ELF phenomena, such as transients, which have frequency components in excess of 3000 Hz have also been examined for their potential contribution to the possible hazard of ELF radiation.

At frequencies above those of interest here, electromagnetic fields propagate by means of tightly coupled electric and magnetic fields (radiation). In such cases, the magnitude of the electric field can be calculated exactly if the magnetic field is known and vice versa. However, in the ELF range, electric and magnetic fields are effectively uncoupled and can be evaluated separately as if they arose from independent sources. At the low frequencies where it is customary to use the quasi-static approximation, the wavelengths of electric and magnetic fields are very large (approximately 5000 km at 60 Hz[1]) in relation to the size and distances of objects of interest (National Radiological Protection Board, 2001). Under these ‘near-field’ conditions (less than one wavelength), electric and magnetic fields do not effectively ‘radiate’ away from the source nor do they occur together in an interrelated way. The field produced by a source is better described as a zone of influence in which the forces on electrical charges oscillate in time and space. More detailed information on physical characteristics may be found elsewhere (e.g. Polk & Postow, 1995).

[1] Wavelength (λ) is the distance in metres travelled by the wave in one period and is related to frequency (f) by $\lambda = c/f$, where c is the speed of light in a vacuum (3×10^8 m/s).

3. Definitions, quantities and units

3.1 Electric fields

An electric field **E** exists in a region of space if a charge experiences an electrical force **F**:

$$\mathbf{F} = q\mathbf{E}$$

where q is the unit positive charge (see Table 1). The direction of the field or force corresponds to the direction that a positive charge would move in the field. Vector quantities are characterized by magnitude and direction and are displayed in bold type. Electric fields are also characterized by the electric flux density or displacement vector **D**, where $\mathbf{D} = \varepsilon\mathbf{E}$ and ε characterizes the material permittivity. The sources of electric fields are unbalanced electrical charges on conductors or other objects. For instance, on a dry winter's day, the action of pulling off a sweater can separate charges on the sweater and hair and the static electric field produced makes the wearer's hair stand on end. Electric utility facilities, including power lines, substations, appliances and building wiring are sources of time-varying electric fields. Electric fields from these sources arise from unbalanced electric charges on energized conductors. The source of the unbalanced charge is the voltage supplied by the power system.

Table 1. Quantities and units

Characteristic	Symbol[a]	SI unit	Symbol
Electric field intensity	**E**	Volt/metre	V/m
Magnetic field intensity	**B**	Tesla	T
Magnetic field	**H**	Ampere/metre	A/m
Current density	**J**	Ampere/metre squared	A/m^2
Frequency	f	Hertz	Hz
Charge density	ρ	Coulomb/metre cubed	C/m^3
Conductivity	σ	Siemens/metre	S/m
Current	I	Ampere	A
Charge	q	Coulomb	C
Force	**F**	Newton	N
Permittivity	ε	Farad per metre	F/m
Permeability	μ	Henry per metre	H/m
Permittivity of free space	ε_o	$\varepsilon_o = 8.854 \times 10^{-12}$ F/m	
Permeability of free space	μ_o	$\mu_o = 12.57 \times 10^{-7}$ H/m	

Note: 1 gauss (G) = 10^{-4} tesla (T); 1 oersted (Oe) = 1 gauss (G) in vacuum or air

[a] Vector quantities are displayed in bold type.

3.2 Current density

Electric fields exert forces on charged particles. In electrically conductive materials, including biological tissues, these forces cause an electric current to flow. The density of this current **J** across a cross-section of tissue is related to the electric field by σ, the electrical conductivity of the medium, as

$$\mathbf{J} = \sigma\mathbf{E}$$

where a homogeneous medium has been assumed.

3.3 Magnetic fields

A magnetic field **H** and associated magnetic flux density **B** exist only if electric charges are in motion, i.e. there is flow of electric current. The relationship between the two descriptions of the field is $\mathbf{B} = \mu\mathbf{H}$, where for most biological materials, $\mu = \mu_o$, where μ_o is the permeability of free space (vacuum, air). The term 'magnetic field' is used in this Monograph as being equivalent to 'magnetic flux density'. Magnetic fields in turn only exert forces on a moving charge, q, as given by the Lorenz force

$$\mathbf{F} = q\mathbf{v} \times \mathbf{B}$$

where the direction of the force is perpendicular to both the velocity **v** and the magnetic flux density **B**.

Static magnetic fields are formed by unidirectional, direct currents (DCs), also called steady currents, and magnetic materials (permanent magnets). Time-varying magnetic fields are produced by the same types of alternating current (AC) sources as electric fields. Time-varying magnetic fields are also sources of electric fields. Similarly, electric fields produce magnetic fields.

3.4 Magnitude

Electric and magnetic fields are vector quantities characterized by a magnitude and direction. Electric fields are most commonly described in terms of the potential difference across a unit distance. A 240-volt source connected to parallel metal plates separated by 1 m produces a field of 240 volts per metre (V/m) between the plates. Large fields are expressed in units of kilovolts per metre (kV/m, 1000 volts per metre).

The magnitude of a magnetic field is described most often by its magnetic flux density **B** in terms of magnetic lines of force per unit area. The units for magnetic flux density are webers per square metre (Wb/m^2) or Système International (SI) units of tesla (T). The equivalent old unit, often seen in the earlier literature, is gauss (G). Units of μT (100 μT = 1 G) are often used to describe ambient strengths of the magnetic field. Less commonly in the biological literature, the magnetic field strength **H** is given in amperes per metre (A/m). Occasionally, the unit of oersted (Oe) is still used.

The magnitudes of electric and magnetic fields are customarily expressed as root-mean-square (rms) values. The rms values of single-frequency sinusoidally varying fields are obtained by dividing the peak amplitude by the square root of two.

3.5 Frequency

Electric and magnetic fields are further determined by the frequency characteristics of their sources. The voltages and currents of the electric power system oscillate at 50 times per second (Hz) (60 Hz in North America) and produce a sinusoidal rise and fall in the magnitude of the associated fields at the same frequency. Electrified rail transport is sometimes powered at frequencies of 25 Hz in the USA (National Research Council, 1997) and $16\,^{2}/_{3}$ Hz in many European countries (National Radiological Protection Board, 2001). The operation of some electrical devices in the power system also produces fields at other frequencies. For example, fields can occur at multiples (harmonics) of the fundamental frequency: at 100, 150, 200 Hz, etc., for a 50-Hz system and at 120, 180, 240 Hz, etc., for a 60-Hz system.

3.6 Polarization

Fields add vectorially: both the magnitude and direction of the field must be considered in combining fields from different sources. A single conductor produces a field vector that changes its direction along a straight line. This is a linearly polarized field and has been used most often in biological studies. Multiple sources that are in phase (synchronized voltage or current waves) also produce linearly polarized fields. However, fields from multiple conductors that are not in phase, such as a three-phase distribution or transmission lines, are not necessarily linearly polarized. In these cases, the field vector is not fixed in space but rotates during a cycle, tracing out an ellipse. The field is then polarized elliptically and the ratio of the minor to major field axis defines the ellipticity or degree of polarization of the field. When the two axes of the ellipse are of equal magnitude, the ellipse forms a circle and the field is described as a circularly polarized field; when one axis is zero the field is linearly polarized.

4. Physical interactions with biological materials

To understand the effects of electric and magnetic fields on animals and humans, their electrical properties, as well as their size and shape, have to be considered with respect to the wavelength of the external field. At ELF, the size of all mammalian and other biological bodies is a very small fraction of the wavelength.

The electrical properties of the body, namely its permittivity and permeability, relate to its interaction with the electric and magnetic fields, respectively. Human and animal bodies consist of numerous tissues, whose electrical properties differ considerably.

The permittivity $\hat{\varepsilon}$ is often written as $\hat{\varepsilon}_r\varepsilon_o$, where $\hat{\varepsilon}_r$ is the relative permittivity and ε_o is permittivity of the vacuum, $8.854.10^{-12}$ farad/m (WHO, 1984). The permittivity determines the interactions with the electric field and the dielectric constant defines the ability to store the field energy.

Similarly, the permeability, $\hat{\mu}$, can be written as $\hat{\mu} = \hat{\mu}_r\mu_o$.

Conductive materials, i.e. those that have free electric charges (e.g. electrons and ions) are also characterized by conductivity, σ. Free charges, if in motion, can interact with both electric and magnetic fields.

Most biological tissues have a permeability equal to that of free space (air, vacuum) (Foster & Schwan, 1989, 1996). Many animal species, including humans, are known to have minuscule amounts of biogenic magnetite (Fe_3O_4) in their brains and other tissues (with permeability $\mu_r \geq 1$) (Kirschvink *et al*., 1992).

The permittivity of biological tissues is to a large extent determined by water and electrolyte contents. Thus, tissues such as blood, muscle, liver and kidneys, which have a higher water content than tissues such as fat and lungs, have higher dielectric constants and conductivities. Both the permittivity and conductivity vary with frequency, and exhibit relaxation phenomena. The physical phenomenon responsible for the dispersion at low frequencies is counterion polarization (Foster & Schwan, 1989, 1996).

At ELF, biological bodies (e.g. humans or animals) can be considered as conductive dielectrics. Induced fields in tissues can be determined solely on the basis of their conductivity. To provide an idea of the range of conductivity values for biological tissues, Table 2 lists the most recently published conductivity measurements (Gandhi *et al*., 2001).

Table 2. Conductivities of various tissues assumed for power-frequency electric and magnetic fields

Tissue	σ (S/m)	Tissue	σ (S/m)
Bladder	0.2	Heart	0.5
Blood	0.7	Kidney	0.09
Bone (cancellous)	0.08	Liver	0.04
Bone (compact)	0.02	Lungs	0.07
Brain (white)	0.06	Muscle	0.24
Cerebrospinal fluid	2.0	Skin	0.04
Eye sclera	0.5	Spinal cord	0.07
Fat	0.02	Testes	0.42

From Gandhi *et al*. (2001)

4.1 Static fields

A static electric field does not penetrate human and animal bodies. The field is always perpendicular to the body surface and induces surface charge density. A sufficiently large charge density may be perceived through its interaction with body hair. Indirect effects associated with induction charges on objects are well known. These range from perception, to pain, to burn resulting from a direct contact or spark discharge. There are well-established thresholds for these effects for human populations (Bernhardt, 1988).

Static magnetic fields can interact with tissues by three mechanisms (Tenforde, 1990, 1992). Firstly, electrodynamic interactions occur with ionic currents, such as blood flow or nerve impulse conduction. This interaction leads to the induction of electric field and electrical potential, e.g. across a blood vessel. This type of interaction is significant only at high flux density ($\geq$ 1 T).

The second interaction mechanism is a magneto-mechanical effect which involves the orientation of certain biological structures in strong magnetic fields (Tenforde, 1992). Sensitivity to low intensity fields is seen in several biological species, such as certain bacteria, fish and birds. Furthermore, magnetite domains have been found in some animals, e.g. bees, tuna, salmon, turtles, pigeons, dolphins and humans. The ability to use these fields for navigation has been demonstrated for some species, e.g. bees. Studies of humans have not yielded any evidence of direction-finding based on the geomagnetic field (Tenforde, 1992).

The third mechanism relates to the Zeeman effect, whereby a magnetic field changes the energy levels of certain molecules. One consequence of the Zeeman effect is to change the probability of recombination of pairs of radicals formed in certain biochemical processes. This may result in changes in the concentration of free radicals, which can be highly reactive. This 'radical-pair mechanism' is well established in magnetochemistry (Hamilton *et al*., 1988; McLauchlan, 1989; Cozens & Scaiano, 1993; Scaiano *et al*., 1994; Grissom, 1995; Mohtat *et al*., 1998), and the relevance to biological effects at low field strengths (e.g. below 500 μT) is currently under investigation (Brocklehurst & McLauchlan, 1996).

Strong static magnetic fields have several indirect effects, such as electromagnetic interference with implanted medical devices (e.g. cardiac pacemakers and defibrillators), and through forces exerted on external and implanted metallic objects. For instance, magnetic field gradients in magnetic resonance imaging facilities are known to turn metallic objects into potentially dangerous projectiles.

4.2 Extremely low-frequency (ELF) fields

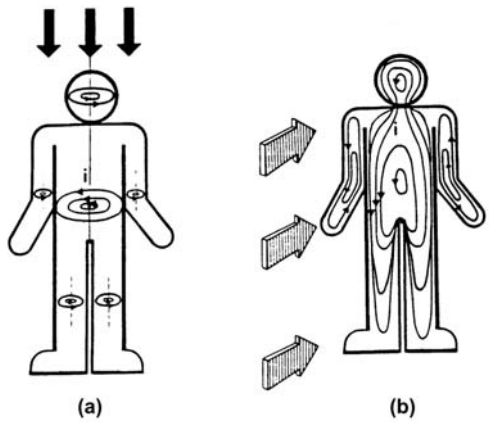
The physical interactions between fields and tissues are governed by Maxwell's equations, but not all tissue components are equally interactive.

At ELFs, the photon energy is exceedingly small, thus a direct interaction causing breakage of chemical bonds and the resultant damage to DNA is not possible. At power frequencies (50 or 60 Hz), the photon energy is about 10^{-12} of the energy required to break the weakest chemical bond (Valberg *et al*., 1997). It is generally agreed that whatever the interaction mechanism, it must be consistent with noise constraints. In principle, meaningful physiological changes can result only if the 'signal' produced by the field exceeds the 'noise' level present in the relevant biological system. For example, in the case of induced currents, the noise level is set by thermal processes (determined in part by kT, where k is Boltzmann's constant and T is the absolute temperature). However, a number of hypotheses listed below have sought to overcome this limitation (e.g. processes involving extremely narrow bandwidths).

The basic interaction mechanism of exposure to magnetic fields is the induction of current density in tissue: currents will always be induced in conductors exposed to time-varying magnetic fields, and current density increases with frequency and body size.

The spatial patterns of the currents induced by electric and magnetic fields are quite different from each other. In an upright human body exposed to a vertical electric field, the induced field and current flow are also vertical. Conversely, in the case of a magnetic field, the current flow forms closed loops, perpendicular to the direction of the magnetic field. General patterns of the current flow induced by exposure to magnetic fields are illustrated in Figure 2.

Figure 2. Induction of eddy currents in the human body perpendicular to (a) a vertical magnetic field and (b) a horizontal magnetic field



From Silny (1986)
In principle, the current density approaches zero at the centre of the loops.

Biological bodies perturb external electric fields. Because the tissue conductivity is low at low frequencies (see Table 2), the induced fields are approximately 10^5–10^8 times lower than the external fields. The perturbation of the external electric field, like the static electric field, induces surface charge on the body surface. The time-varying

surface charge may cause hair oscillation, particularly in some laboratory animals (Tenforde & Kaune, 1987; Tenforde, 1991). Humans can detect 60-Hz electric fields through hair stimulation at about 20 kV/m, while the threshold is lower for some furry rodents (Tenforde, 1991). In contrast, because tissue permeability to magnetic fields is the same as that of free space, these fields penetrate the body with virtually no distortion. The magnitude of the induced electric fields depends mostly on the body size and shape, and the field orientation. The conductivities of various tissues have a lesser influence on the induced electric fields. Extensive data are available on induced electric field and current density values for exposure to ELF electric and magnetic fields, as outlined in detail in section 1.3.2.

A well-established physical mechanism of interaction at the cellular level is the stimulation of excitable cells, such as those in nerves, muscles and the heart which occurs when the electric field in the tissue exceeds a threshold value of V_m (the potential across a cell membrane). Once this threshold is exceeded, the nerve or muscle cell propagates an action potential. The threshold V_m depends on cell type, dimension and shape as well as the signal frequency, duration and waveform (e.g. monopolar pulse, bipolar pulse, sinusoid, single pulse or repeated pulses). Cell excitation and action potential propagation are complex non-linear processes (Plonsey & Barr, 1988; Reilly, 1992; Malmivuo & Plonsey, 1995). A typical value for V_m is 20 mV for the optimal pulse shape, duration and an appropriate polarity causing depolarization (Reilly, 1992, 1998).

To induce neural or cardiac stimulation by 50- or 60-Hz fields, very strong external electric or magnetic fields are required: the reported thresholds are above 1 A/m^2 (Bailey *et al.*, 1997).

Experimental evidence and thresholds have been determined in human volunteers for magnetic stimulation of the visual system causing phosphenes, which are weak visual sensations (Lövsund *et al.*, 1979, 1980). The lowest threshold magnetic field strength is 8 mT (in darkness) at 20 Hz. The threshold increases for higher and lower frequencies of the magnetic field as well as when the background is illuminated. Phosphenes have also been produced by direct electrostimulation. Again, the threshold was observed for 20 Hz and increases at higher and lower frequencies. It is believed that the effect is a result of the interaction of the induced current with electrically excitable cells in the retina.

The above mechanisms have a well-understood physical basis.

Several other physical interactions have been examined theoretically. Forces exerted by the field on ions and charged molecules have been compared with forces generated by biological structures. For example, an electric field of 5 mV/m in tissue produces a force on a charged molecule of 2×10^{-5} piconewton (pN). In comparison, biological activity reported in various studies is associated with forces above 1 pN, and typically above 10 pN (Valberg *et al.*, 1997).

At ELF, the radical-pair mechanism described above for static magnetic fields still applies. This is because the period of ELF fields, ~ 20 ms, is long compared to the

lifetime of radical pairs (nano- to microseconds). Therefore, the radical pairs experience the instantaneous combined static and ELF magnetic fields.

In addition, a number of other mechanisms have been suggested, for which either the physical basis is not yet clear or the experimental evidence for relevance to the biological effects of ELF fields is still being sought.

From present knowledge, it is clear that there are a number of mechanisms theoretically capable of explaining the occurrence of biological effects at high field strengths. Electric fields induced in tissue are known to produce effects at levels corresponding to an external field of above 0.4 mT and 5–10 kV/m (Bernhardt, 1988).

5. Studies of ELF electric and magnetic fields relevant to carcinogenicity

Studies on the possible carcinogenic effects of ELF electric and magnetic fields are hampered by complications, or lack of information, at almost every level. Issues of EMF exposure which affect the interpretation of referent epidemiological studies are discussed in section 2.1.1. High-quality studies of cancer induced in experimental animals by ELF electric and magnetic fields have been initiated fairly recently. Attempts have been made to examine carcinogenesis associated with exposure to electric and magnetic fields in the context of a multistep process of cancer causation. However, the manner in which these fields might interact with other stimuli, including carcinogens such as X-rays, ultraviolet radiation and chemicals may include as yet undefined processes. Studies of carcinogenesis in experimental animals, and their implications are discussed in section 3.

Studies of the effects of ELF electric and magnetic fields on cells in culture, or using simpler biological systems have attempted to characterize particular molecular processes. Sufficient studies are available to identify other limitations on any simple correlation between ‘conventional’ carcinogens and the putative hazard under investigation. Firstly, it is apparent that many systems fail to provide any evidence of a treatment-related effect. Secondly, when such effects are observed, other laboratories have often been unable to reproduce the observation. Such failure to reproduce extends across a range of phenomena, and often involves numerous investigators. It is not, therefore, a simple difference between two centres and is unlikely to be explicable simply as the result of a lack of care by one or more of the laboratories concerned, but may be a consequence of an inability to reproduce exactly the electric and magnetic fields to which cells or whole animals have been exposed in a particular study.

The many parameters known to characterize electric and magnetic fields have been outlined above. Most often, an experimental field is described by reference to the intensity alone (usually specified in V/m for electric fields or Tesla for magnetic

fields). Other as yet unspecified characteristics of the field may contribute, if not be critical to, particular experimental results.

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STATIC AND EXTREMELY LOW-FREQUENCY (ELF) ELECTRIC AND MAGNETIC FIELDS

1. Sources, Exposure and Exposure Assessment

1.1 Sources

1.1.1 *Natural magnetic and electric fields*

Humans are exposed daily to electric and magnetic fields from both natural and man-made sources. The strengths of fields from man-made sources can exceed those from natural sources by several orders of magnitude.

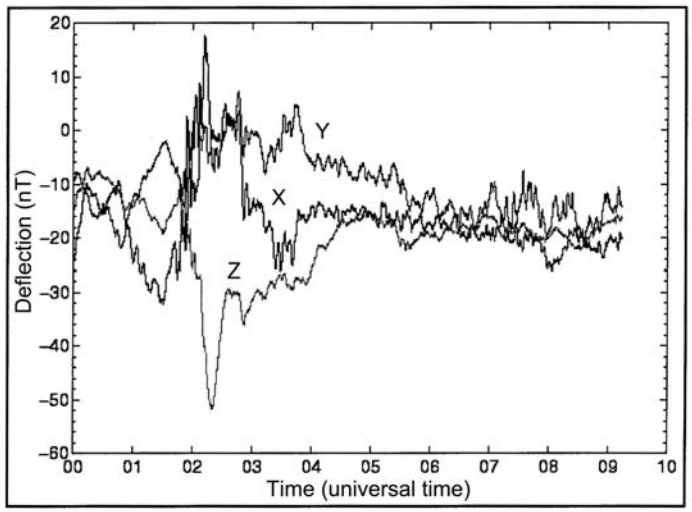
The existence of the geomagnetic field has been known since ancient times. The geomagnetic field is primarily dipolar in nature. The total field intensity diminishes from its maxima of about 60 μT at the magnetic poles, to a minimum of about 30 μT near the equator (König *et al.*, 1981). In temperate latitudes, the geomagnetic field, at sea-level, is approximately 45–50 μT whereas in regions of southern Brazil, flux densities as low as 24 μT have been reported (Hansson Mild, 2000).

The geomagnetic field is not constant but fluctuates continuously and is subject to diurnal, lunar and seasonal variations (Strahler, 1963; König *et al*., 1981). More information on this subject is available (Dubrov, 1978) and in databases on the Web (e.g. National Geophysical Data Center).

There are also short-term variations associated with ionospheric processes. When the solar wind carries protons and electrons towards the earth, phenomena such as the Northern Lights, and rapid fluctuations in the intensity of the geomagnetic field occur. Figure 1 shows a 9-hour recording made at the Kiruna observatory in Sweden in January 2002. The variation may be large and can sometimes range from 0.1 μT to 1 μT within a few minutes. Such rapid variations are rare and correlated with the solar cycle. More commonly, variations of similar magnitude occur over a longer period of time. Despite these variations, the geomagnetic field should always be considered as a static field.

The atmosphere also has an electric field that is directed radially because the earth is negatively charged. The field strength depends to some extent on geographical latitude; it is lowest towards the poles and the equator and highest in the temperate latitudes. The average strength is around 100 V/m in fair weather, although it may range from 50–500 V/m depending on weather, altitude, time of day and season. During precipitation and bad weather, the values can change considerably, varying over a range of ± 40 000 V/m (König *et al*., 1981). The average atmospheric electric field is not very different from that produced in most dwellings by typical 50- or 60-Hz electric field

Figure 1. Magnetogram recording from a geomagnetic research station in Kiruna, Sweden



Kiruna magnetogram 2002-01-28, 09:13:35
Real-time geomagnetogram recordings can be seen at (http://www.irf.se/mag). The recordings are made in three axes: X, north, Y, east, and Z, down. The trace shown is the deflection from the mean value of the magnetic field at this location.

power sources (National Radiological Protection Board, 2001), except when measurements are made very close to electric appliances.

The electromagnetic processes associated with lightning discharges are termed *atmospherics* or '*sferics*' for short. They occur in the ELF range and at higher frequencies (König *et al.*, 1981). Each second, about 100 lightning discharges occur worldwide and can be detected thousands of kilometres away (Hansson Mild, 2000).

1.1.2 *Man-made fields and exposure*

People are exposed to electric and magnetic fields arising from a wide variety of sources which use electrical energy at various frequencies. Man-made sources are the dominant sources of exposure to time-varying fields. At power frequencies (a term that encompasses 50 and 60 Hz and their harmonics), man-made fields are many thousands of times greater than natural fields arising from either the sun or the earth.

When the source is spatially fixed and the source current and/or electrical potential difference is constant in time, the resulting field is also constant, and is referred to as static, hence the terms *magnetostatic* and *electrostatic*. Electrostatic fields are produced by fixed potential differences. Magnetostatic fields are established by permanent magnets and by steady currents. When the source current or voltage varies in time, for example, in a sinusoidal, pulsed or transient manner, the field varies proportionally.

In practice, the waveform may be a simple sinusoid or may be more complex, indicating the presence of harmonics. Complex waveforms are also observed when transients occur. Transients and interruptions, either in the electric power source or in the load, result in a wide spectrum of frequencies that may extend above several kHz (Portier & Wolfe, 1998).

Power-frequency electric and magnetic fields are ubiquitous and it is important to consider the possibilities of exposure both at work and at home. Epidemiological studies may focus on particular populations because of their proximity to specific sources of exposure, such as local power lines and substations, or because of their use of electrical appliances. These sources of exposure are not necessarily the dominant contributors to a person's time-weighted average exposure if this is indeed the parameter of interest for such studies. Various other metrics have been proposed that reflect aspects of the intermittent and transient characteristics of fields. Man-made sources and their associated fields are discussed more fully elsewhere (see National Radiological Protection Board, 2001).

(*a*) *Residential exposure*

There are three major sources of ELF electric and magnetic fields in homes: multiple grounded current-carrying plumbing and/or electric circuits, appliances and nearby power lines, including lines supplying electricity to individual homes (known as service lines, service drops or drop lines).

(i) *Background exposure*

Extremely low-frequency magnetic fields in homes arise mostly from currents flowing in the distribution circuits, conducting pipes and the electric ground, and from the use of appliances. The magnetic fields are partially cancelled if the load current matches the current returning via the neutral conductor. The cancellation is more effective if the conductors are close together or twisted. In practice, return currents do not flow exclusively through the associated neutral cable, but are able to follow alternative routes because of interconnected neutral cables and multiple earthing of neutral conductors. This diversion of current from the neutral cable associated with a particular phase cable results in unbalanced currents producing a net current that gives rise to a residual magnetic field. These fields produce the general background level inside and outside homes (National Radiological Protection Board, 2001). The magnetic fields in the home that arise from conductive plumbing paths were noted by Wertheimer *et al*. (1995) to "provide opportunity for frequent, prolonged encounters with 'hot spots' of unusually high intensity field — often much higher than the intensity cut-points around [0.2 or 0.3 μT] previously explored".

The background fields in homes have been measured in many studies. Swanson and Kaune (1999) reviewed 27 papers available up to 1997; other significant studies have been reported by Dockerty *et al*. (1998), Zaffanella and Kalton (1998), McBride *et al*. (1999), UK Childhood Cancer Study Investigators (UKCCSI) (1999) and Schüz

et al. (2000). The distribution of background field intensities in a population is usually best characterized by a log-normal distribution. The mean field varies from country to country, as a consequence of differences in supply voltages, per-capita electricity consumption and wiring practices, particularly those relating to earthing of the neutral. Swanson and Kaune (1999) found that the distribution of background fields, measured over 24 h or longer, in the USA has a geometric mean of 0.06–0.07 μT, corresponding to an arithmetic mean of around 0.11 μT, and that fields in the United Kingdom are lower (geometric mean, 0.036–0.039 μT; arithmetic mean, approximately 0.05 μT), but found insufficient studies to draw firm conclusions on average fields in other European countries. Wiring practices in some countries such as Norway lead to particularly low field strengths in dwellings (Hansson Mild *et al*., 1996).

In addition to average background fields, there is interest in the percentages of homes with fields above various cut-points. Table 1 gives the magnetic field strengths measured over 24 or 48 h in the homes of control subjects from four recent large epidemiological studies of children.

Few homes are exposed to significant fields from high-voltage power lines (see below). Even in homes with fields greater than 0.2 or 0.4 μT, high-voltage power lines are not the commonest source of the field.

The electric field strength measured in the centre of a room is generally in the range 1–20 V/m. Close to domestic appliances and cables, the field strength may increase to a few hundred volts per metre (National Radiological Protection Board, 2001).

Table 1. Measured exposure to magnetic fields in residential epidemiological studies

Study	Country	No. of control children having long-term measurements	Percentage of controls exposed to field strengths greater than	
			0.2 μT	0.4 μT
Linet *et al*. (1997)[a]	USA	530	9.2	0.9
McBride *et al*. (1999)[a]	Canada	304	11.8	3.3
UKCCSI (1999)[a]	United Kingdom	2224	1.5	0.4
Schüz *et al*. (2001a)[b]	Germany	1301	1.4	0.2

UKCCSI, UK Childhood Cancer Study Investigators

[a] Percentages calculated from data on geometric means from Ahlbom *et al*. (2000). (The results presented by Dockerty *et al*. (1999) have not been included as the numbers are too small to be meaningful at these field strengths.)

[b] Percentages calculated from medians from original data. The medians are expected to be very similar to the geometric means.

(ii) *Fields from appliances*

The highest magnetic flux densities to which most people are exposed in the home arise close to domestic appliances that incorporate motors, transformers and heaters (for most people, the highest fields experienced from domestic appliances are also higher than fields experienced at work and outside the home). The flux density decreases rapidly with distance from appliances, varying between the inverse square and inverse cube of distance, and at a distance of 1 m the flux density will usually be similar to background levels. At a distance of 3 cm, magnetic flux densities may be several hundred microtesla or may even approach 2 mT from devices such as hair dryers and can openers, although there can be wide variations in fields at the same distance from similar appliances (National Radiological Protection Board, 2001).

Exposure to magnetic fields from home appliances must be considered separately from exposure to fields due to power lines. Power lines produce relatively low-intensity, small-gradient fields that are always present throughout the home, whereas fields produced by appliances are invariably more intense, have much steeper gradients, and are, for the most part, experienced only sporadically. The appropriate way of combining the two field types into a single measure of exposure depends critically on the exposure metric considered.

Various features of appliances determine their potential to make a significant contribution to the fields to which people are exposed, and epidemiological studies of appliances have focused on particular appliances chosen for the following reasons:

- Use particularly close to or touching the body. Examples include hair dryers, electric shavers, electric drills and saws, and electric can openers or food mixers.
- Use at moderately close distances for extended periods of time. Examples include televisions and video games, sewing machines, bedside clocks and clock radios and night storage heaters, if, for example, they are located close to the bed.
- Use while in bed, combining close proximity with extended periods of use. Examples include electric blankets and water beds (which may or may not be left on overnight).
- Use over a large part of the home. Examples include underfloor electric heating.

Table 2 gives values of broadband magnetic fields at various distances from domestic appliances in use in the United Kingdom (Preece *et al*., 1997). The magnetic fields were calculated from a mathematical model fitted to actual measurements made on the numbers of appliances shown in the Table. Gauger (1985) and Zaffanella & Kalton (1998) reported narrow band and broadband data, respectively, for the USA. Florig and Hoburg (1990) characterized fields from electric blankets, using a three-dimensional computer model and Wilson *et al*. (1996) used spot measurements made in the home and in the laboratory. They reported that the average magnetic fields to which

Table 2. Resultant broadband magnetic field calculated at 5, 50 and 100 cm from appliances for which valid data could be derived on the basis of measured fields at 5, 30, 60 and 100 cm

		Magnetic field (μT) at discrete distances from the surface of appliances computed from direct measurements					
Appliance type	No.	5 cm	± SD	50 cm	± SD	100 cm	± SD
Television	73	2.69	1.08	0.26	0.11	0.07	0.04
Kettle, electric	49	2.82	1.51	0.05	0.06	0.01	0.02
Video-cassette recorder	42	0.57	0.52	0.06	0.05	0.02	0.02
Vacuum cleaner	42	39.53	74.58	0.78	0.74	0.16	0.12
Hair dryer	39	17.44	15.56	0.12	0.10	0.02	0.02
Microwave oven	34	27.25	16.74	1.66	0.63	0.37	0.14
Washing machine	34	7.73	7.03	0.96	0.56	0.27	0.14
Iron	33	1.84	1.21	0.03	0.02	0.01	0.00
Clock radio	32	2.34	1.96	0.05	0.05	0.01	0.01
Hi-fi system	30	1.56	4.29	0.08	0.14	0.02	0.03
Toaster	29	5.06	2.71	0.09	0.08	0.02	0.02
Central heating boiler	26	7.37	10.10	0.27	0.26	0.06	0.05
Central heating timer	24	5.27	7.05	0.14	0.17	0.03	0.04
Fridge/freezer	23	0.21	0.14	0.05	0.03	0.02	0.01
Radio	23	3.00	3.26	0.06	0.04	0.01	0.01
Central heating pump	21	61.09	59.58	0.51	0.47	0.10	0.10
Cooker	18	2.27	1.33	0.21	0.15	0.06	0.04
Dishwasher	13	5.93	4.99	0.80	0.46	0.23	0.13
Freezer	13	0.42	0.87	0.04	0.02	0.01	0.01
Oven	13	1.79	0.89	0.39	0.23	0.13	0.09
Shower, electric	12	30.82	35.04	0.44	0.75	0.11	0.25
Burglar alarm	10	6.20	5.21	0.18	0.11	0.03	0.02
Food processor	10	12.84	12.84	0.23	0.23	0.04	0.04
Extractor fan	9	45.18	107.96	0.50	0.93	0.08	0.14
Cooker hood	9	4.77	2.53	0.26	0.10	0.06	0.02
Speaker	8	0.48	0.67	0.07	0.13	0.02	0.04
Hand blender	8	76.75	87.09	0.97	1.05	0.15	0.16
Tumble dryer	7	3.93	5.45	0.34	0.42	0.10	0.10
Food mixer	6	69.91	69.91	0.69	0.69	0.11	0.11
Fish-tank pump	6	75.58	64.74	0.32	0.09	0.05	0.01
Computer	6	1.82	1.96	0.14	0.07	0.04	0.02
Electric clock	6	5.00	4.15	0.04	0.00	0.01	0.00
Electric knife	5	27.03	13.88	0.12	0.05	0.02	0.01
Hob	5	2.25	2.57	0.08	0.05	0.01	0.01
Deep-fat fryer	4	4.44	1.99	0.07	0.01	0.01	0.00
Tin/can opener	3	145.70	106.23	1.33	1.33	0.20	0.21
Fluorescent light	3	5.87	8.52	0.15	0.20	0.03	0.03
Fan heater	3	3.64	1.41	0.22	0.18	0.06	0.06
Liquidizer	2	3.28	1.19	0.29	0.35	0.09	0.12

Table 2 (contd)

	Magnetic field (μT) at discrete distances from the surface of appliances computed from direct measurements						
Appliance type	No.	5 cm	± SD	50 cm	± SD	100 cm	± SD
Bottle sterilizer	2	0.41	0.17	0.01	0.00	0.00	0.00
Coffee maker	2	0.57	0.03	0.06	0.07	0.02	0.02
Shaver socket	2	16.60	1.24	0.27	0.01	0.04	0.00
Coffee mill	1	2.47		0.28		0.07	
Shaver, electric	1	164.75		0.84		0.12	
Tape player	1	2.00		0.24		0.06	

From Preece *et al.* (1997)

the whole body is exposed are between 1 and 3 μT. From eight-hour measurements, Lee *et al.* (2000) estimated that the time-weighted average magnetic field exposures from overnight use of electric blankets ranged between 0.1 and 2 μT.

Measurements of personal exposure are expected to be higher than measurements of background fields because they include exposures from sources such as appliances. Swanson and Kaune (1999) found that in seven studies which measured personal exposure and background fields for the same subjects, the ratio varied from 1.0 to 2.3 with an average of 1.4.

(iii) *Power lines*

Power lines operate at voltages ranging from the domestic supply voltage (120 V in North America, 220–240 V in Europe) up to 765 kV in high-voltage power lines (WHO, 1984). At higher voltages, the main source of magnetic field is the load current carried by the line. Higher voltage lines are usually also capable of carrying higher currents. As the voltage of the line and, hence, in general, the current carried, and the separation of the conductors decrease, the load current becomes a progressively less important source of field and the net current, as discussed in (i) above, becomes the dominant source. It is therefore convenient to treat high-voltage power lines (usually taken to mean 100 kV or 132 kV, also referred to as transmission lines) as a separate source of field (Merchant *et al.*, 1994; Swanson, 1999).

High-voltage power lines in different countries follow similar principles, but with differences in detail so that the fields produced are not identical (power-line design as it affects the fields produced was reviewed by Maddock, 1992). For example, high-voltage power lines in the United Kingdom can have lower ground clearances and can carry higher currents than those in some other countries, leading to higher fields under the lines. When power lines carry two or more circuits, there is a choice as to the physical distribution of the various wires on the towers. An arrangement called ‘transposed phasing’, in which the wires or bundles of wire — phases — in the circuit

on one side of the tower have the opposite order to those on the other side, results in fields that decrease more rapidly with distance from the lines than the alternatives (Maddock, 1992). Transposed phasing is more common in the United Kingdom than, for example, in the USA.

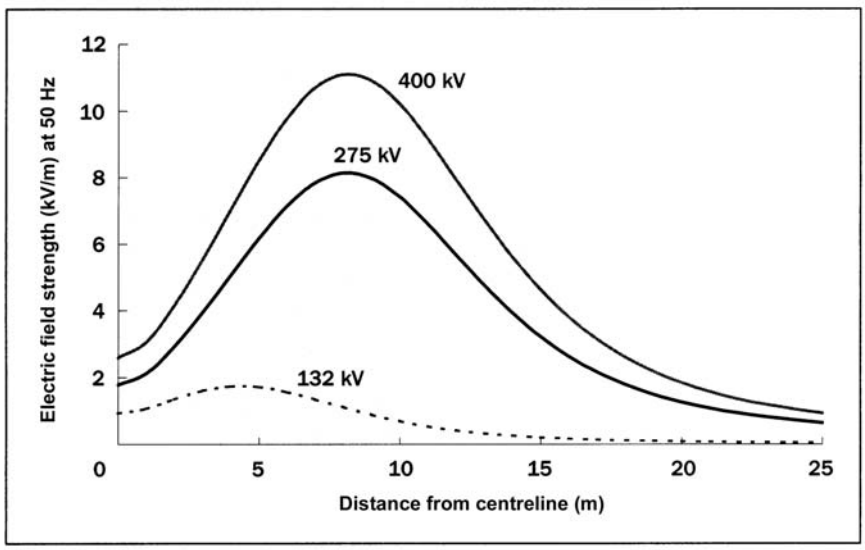
In normal operation, high-voltage power lines have higher ground clearances than the minimum permitted, and carry lower currents than the maximum theoretically possible. Therefore, the fields present in normal operation are substantially lower than the maxima theoretically possible.

Electric fields

High-voltage power lines give rise to the highest electric field strengths that are likely to be encountered by people. The maximum unperturbed electric field strength immediately under 400-kV transmission lines is about 11 kV/m at the minimum clearance of 7.6 m, although people are generally exposed to fields well below this level. Figure 2 gives examples of the variation of electric field strength with distance from the centreline of high-voltage power lines with transposed phasing in the United Kingdom. At 25 m to either side of the line, the field strength is about 1 kV/m (National Radiological Protection Board, 2001).

Objects such as trees and other electrically grounded objects have a screening effect and generally reduce the strength of the electric fields in their vicinity. Buildings attenuate electric fields considerably, and the electric field strength may be one to three

Figure 2. Electric fields from high-voltage overhead power lines



From National Radiological Protection Board (2001)

orders of magnitude less inside a building than outside it. Electric fields to which people are exposed inside buildings are generally produced by internal wiring and appliances, and not by external sources (National Radiological Protection Board, 2001).

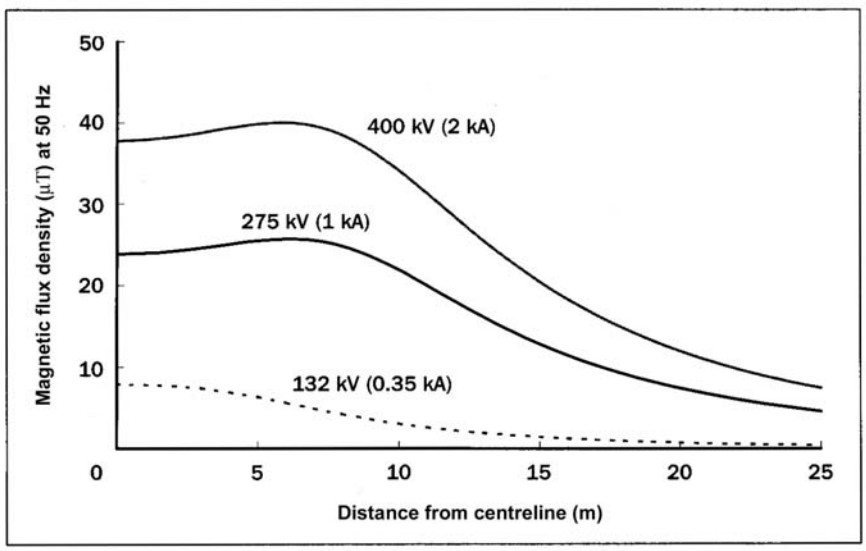
Magnetic fields

The average magnetic flux density measured directly beneath overhead power lines can reach 30 μT for 765-kV lines and 10 μT for the more common 380-kV lines (Repacholi & Greenebaum, 1999). Theoretical calculations of magnetic flux density beneath the highest voltage power line give ranges of up to 100 μT (National Radiological Protection Board, 2001). Figure 3 gives examples of the variation of magnetic flux density with distance from power lines in the United Kingdom. Currents (and hence the fields produced) vary greatly from line to line because power consumption varies with time and according to the area in which it is measured.

Magnetic fields generally fall to background strengths at distances of 50–300 m from high-voltage power lines depending on the line design, current and the strength of background fields in the country concerned (Hansson Mild, 2000). Few people live so close to high-voltage power lines (see Table 3); meaning that these power lines are a major source of exposure for less than 1% of the population according to most studies (see Table 4).

In contrast to electric fields for which the highest exposure is likely to be experienced close to high-voltage power lines, the highest magnetic flux densities are

Figure 3. Magnetic fields from high-voltage overhead power lines



From National Radiological Protection Board (2001)

Table 3. Percentages of people in certain countries within various distances of high-voltage power lines

Country (reference)	No. of subjects	Voltages of power lines included (kV)	Distance (m)	Subjects within this distance	
				No.	%
Canada (McBride *et al*., 1999)	399[a]	≥ 50	50	4	1.00
			100	7	1.75
Denmark (Olsen *et al*., 1993)	6495[b]	132–150	75	28	0.43
		50–60	35	22	0.34
					0.46
		50–440	150	52	0.80
United Kingdom (Swanson, 1999)	22 million[c]	≥ 275	50		0.07
			100		0.21
United Kingdom (UKCCSI, 2000a)	3390[a]	≥ 66	50	9	0.27
			120	35	1.03
		≥ 275	50	3	0.09
			120	9	0.27
USA (Kleinerman *et al*., 2000)	405[a]	≥ 50[d] power line	40	98	24.2
		transmission line	40	20	4.94

UKCCSI, UK Childhood Cancer Study Investigators

[a] Controls from epidemiological study of children

[b] Cases and controls from epidemiological study of children

[c] All homes in England and Wales (Source: Department of Transport, Local Government and the Regions; National Assembly for Wales, 1998, http://www.statistics.gov.uk/statbase/Expodata/Spreadsheets/D4524.xls)

[d] Not stated in Kleinerman *et al*. (2000), assumed to be the same as Wertheimer & Leeper (1979)

more likely to be encountered in the vicinity of appliances or types of equipment that carry large currents (National Radiological Protection Board, 2001).

Direct current lines

Some high-voltage power lines have been designed to carry direct current (DC), therefore producing both electrostatic and magnetostatic fields. Under a 500-kV DC transmission line, the static electric field can reach 30 kV/m or higher, while the magnetostatic field from the line can average 22 μT which adds vectorially to the earth's field (Repacholi & Greenebaum, 1999).

Table 4. Percentages of people in various countries living in homes in which high-voltage power lines produce magnetic fields in excess of specified values

Country (reference)	No. of subjects	Voltages of power lines included (kV)	Measured field (μT)	Subjects whose homes exceed the measured field	
				No.	%
Denmark (Olsen *et al*., 1993)	4788[a]	≥ 50	0.25	11	0.23
			0.4	3	0.06
Germany (Schüz *et al*., 2000)	1835[b]	≥ 123	0.2	8	0.44
United Kingdom (UKCCSI, 2000a)	3390[a]	≥ 66[c]	0.2	11	0.32
			0.4	8	0.24

UKCCSI, UK Childhood Cancer Study Investigators
[a] Controls from epidemiological study of children
[b] Cases and controls from epidemiological study of children
[c] Probably over 95% were ≥ 132 kV

(iv) *Substations*

Outdoor substations normally do not increase residential exposure to electric and magnetic fields. However, substations inside buildings may result in exposure to magnetic fields at distances less than 5–10 m from the stations (National Radiological Protection Board, 2001). On the floor above a station, flux densities of the order of 10–30 μT may occur depending on the design of the substation (Hansson Mild *et al.*, 1991). Normally, the main sources of field are the electrical connections (known as busbars) between the transformer and the other parts of the substation. The transformer itself can also be a contributory source.

(v) *Exposure to ELF electric and magnetic fields in schools*

Exposure to ELF electric and magnetic fields while at school may represent a significant fraction of a child's total exposure. A study involving 79 schools in Canada took a total of 43 009 measurements of 60-Hz magnetic fields (141–1543 per school). Only 7.8% of all the fields measured were above 0.2 μT. For individual schools, the average magnetic field was 0.08 μT (SD, 0.06 μT). In the analysis by use of room, only typing rooms had magnetic fields that were above 0.2 μT. Hallways and corridors were above 0.1 μT and all other room types were below 0.1 μT. The percentage of classrooms above 0.2 μT was not reported. Magnetic fields above 0.2 μT were mostly associated with wires in the floor or ceiling, proximity to a room containing electrical appliances or movable sources of magnetic fields such as electric typewriters,

computers and overhead projectors. Eight of the 79 schools were situated near high-voltage power lines. The survey showed no clear difference in overall magnetic field strength between the schools and domestic environments (Sun *et al.*, 1995).

Kaune *et al.* (1994) measured power-frequency magnetic fields in homes and in the schools and daycare centres of 29 children. Ten public shools, six private schools and one daycare centre were included in the study. In general, the magnetic field strengths measured in schools and daycare centres were smaller and less variable than those measured in residential settings.

The UK Childhood Cancer Study Investigators (UKCCSI) (1999) carried out an epidemiological study of children in which measurements were made in schools as well as homes. Only three of 4452 children aged 0–14 years who spent 15 or more hours per week at school during the winter, had an average exposure during the year above 0.2 μT as a result of exposure at school.

In a preliminary report reviewed elsewhere (Portier & Wolfe, 1998), Neutra *et al.* (1996) reported a median exposure level of 0.08 μT for 163 classrooms at six California schools, with approximately 4% of the classrooms having an average magnetic field in excess of 0.2 μT. These fields were mainly due to ground currents on water pipes, with nearby distribution lines making a smaller contribution. [The Working Group noted that no primary publication was available.] The study was subsequently extended and an executive summary was published in an electronic form, which is available at www.dhs.ca.gov/ehib/emf/school_exp_ass_exec.pdf

(*b*) *Occupational exposure*

Exposure to magnetic fields varies greatly across occupations. The use of personal dosimeters has enabled exposure to be measured for particular types of job. Table 5 (Portier & Wolfe, 1998) lists the time-weighted average exposure to magnetic fields for selected job classifications. In some cases the standard deviations are large. This indicates that there are instances in which workers in these categories are exposed to far stronger fields than the means listed here.

Floderus *et al.* (1993) investigated sets of measurements made at 1015 different workplaces using EMDEX (electric and magnetic field digital exposure system)-100 and EMDEX-C personal dosimeters. This study covered 169 different job categories and participants wore the dosimeters for a mean duration of 6.8 h. The distribution of all 1-s sampling period results for 1015 measurements is shown in Figure 4. The most common measurement was 0.05 μT and measurements above 1 μT were rare. It should be noted that the response of the EMDEX-C is non-linear over a wide frequency range. For example, the railway frequency in Sweden is $16\ ^{2}/_{3}$ Hz, which means that the measurements obtained with the EMDEX are underestimates of the exposure.

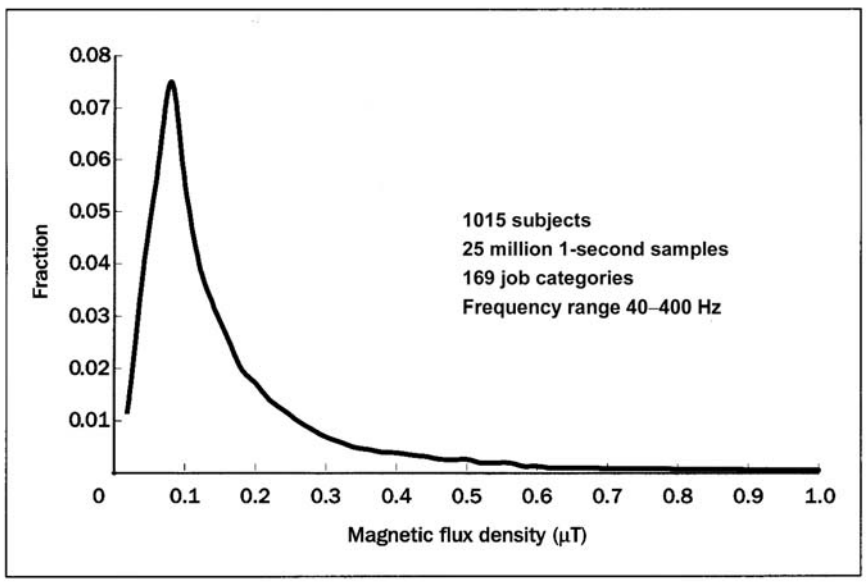
It can be seen from Table 5 that workers in certain occupations are exposed to elevated magnetic fields. Some of the more significant occupations are considered below.

Table 5. Time-weighted average exposure to magnetic fields by job title

Occupational title	Average exposure (μT)	Standard deviation
Train (railroad) driver	4.0	NR
Lineman	3.6	11
Sewing machine user	3.0	0.3
Logging worker	2.5	7.7
Welder	2.0	4.0
Electrician	1.6	1.6
Power station operator	1.4	2.2
Sheet metal worker	1.3	4.2
Cinema projectionist	0.8	0.7

Modified from Portier & Wolfe (1998)
NR, not reported

Figure 4. Distribution of all occupational magnetic field samples



Modified from National Radiological Protection Board (2001) (original figure from Floderus *et al.*, 1993)
The distribution should not be interpreted as a distribution of results for individuals.

(i) *The electric power industry*

Strong magnetic fields are encountered mainly in close proximity to high currents (Maddock, 1992). In the electric power industry, high currents are found in overhead lines and underground cables, and in busbars in power stations and substations. The busbars close to generators in power stations can carry currents up to 20 times higher than those typically carried by the 400-kV transmission system (Merchant *et al.*, 1994).

Exposure to the strong fields produced by these currents can occur either as a direct result of the job, e.g. a lineman or cable splicer, or as a result of work location, e.g. when office workers are located on a power station or substation site. It should be noted that job categories may include workers with very different exposures, e.g. linemen working on live or dead circuits. Therefore, although reporting magnetic-field exposure by job category is useful, a complete understanding of exposure requires a knowledge of the activities or tasks and the location as well as measurements made by personal exposure meters.

The average magnetic fields to which workers are exposed for various jobs in the electric power industry have been reported as follows: 0.18–1.72 μT for workers in power stations, 0.8–1.4 μT for workers in substations, 0.03–4.57 μT for workers on lines and cables and 0.2–18.48 μT for electricians (Portier & Wolfe, 1998; National Radiological Protection Board, 2001).

(ii) *Arc and spot welding*

In arc welding, metal parts are fused together by the energy of a plasma arc struck between two electrodes or between one electrode and the metal to be welded. A power-frequency current usually produces the arc but higher frequencies may be used in addition to strike or to maintain the arc. A feature of arc welding is that the welding cable, which can carry currents of hundreds of amperes, can touch the body of the operator. Stuchly and Lecuyer (1989) surveyed the exposure of arc welders to magnetic fields and determined separately the exposure at 10 cm from the head, chest, waist, gonads, hands and legs. Whilst it is possible for the hand to be exposed to fields in excess of 1 mT, the trunk is typically exposed to several hundred microtesla. Once the arc has been struck, these welders work with comparatively low voltages and this is reflected in the electric field strengths measured; i.e. up to a few tens of volts per metre (National Radiological Protection Board, 2001).

Bowman *et al*. (1988) measured exposure for a tungsten–inert gas welder of up to 90 μT. Similar measurements reported by the National Radiological Protection Board indicate magnetic flux densities of up to 100 μT close to the power supply, 1 mT at the surface of the welding cable and at the surface of the power supply and 100–200 μT at the operator position (National Radiological Protection Board, 2001). London *et al.* (1994) reported the average workday exposure of 22 welders and flame cutters to be much lower (1.95 μT).

(iii) *Induction furnaces*

Measurements on induction furnaces and heaters operating in the frequency range from 50 Hz to 10 kHz have been reported (Lövsund *et al*., 1982) and are summarized in Table 6. The field strengths decrease rapidly with distance from the coils and do not reflect whole-body exposure. However, in some cases, whole-body exposure occurs. Induction heater operators experience short periods of exposure to relatively strong fields as the induction coils are approached (National Radiological Protection Board, 2001).

Table 6. Frequency and magnetic flux densities from induction furnaces

Type of machine	No.	Frequency band	Magnetic flux density (mT): measured ranges
Ladle furnace in conjunction with 1.6-Hz magnetic stirrer, measurements made at 0.5–1 m from furnace	1	1.6 Hz, 50 Hz	0.2–10
Induction furnace,			
at 0.6–0.9 m	2	50 Hz	0.1–0.9
at 0.8–2.0 m	5	600 Hz	0.1–0.9
Channel furnace, at 0.6–3.0 m	3	50 Hz	0.1–0.4
Induction heater, at 0.1–1.0 m	5	50 Hz–10 kHz	1–60

Modified from Lövsund *et al*. (1982)

(iv) *Electrified transport*

Electricity is utilized in various ways in public transport. The power is supplied as DC or at alternating frequencies up to those used for power distribution. Many European countries such as Austria, Germany, Norway, Sweden and Switzerland have systems that operate at $16\ ^{2}/_{3}$ Hz. Most of these systems use a DC traction motor, and rectification is carried out either on-board or prior to supply. On-board rectification usually requires a smoothing inductor, a major source of static and 100-Hz alternating magnetic fields. For systems that are supplied with nominal DC there is little smoothing at the rectification stage, resulting in a significant alternating component in the 'static' magnetic fields (National Radiological Protection Board, 2001).

On Swedish trains, Nordenson *et al*. (2001) found values ranging from 25 to 120 μT for power-frequency fields in the driver's cab, depending on the type (age and model) of locomotive. Typical daily average exposures were in the range of 2–15 μT.

Other forms of transport, such as aeroplanes and electrified road vehicles are also expected to increase exposure, but have not been investigated extensively.

(v) *Use of video display terminals*

Occupational exposure to ELF electric and magnetic fields from video display terminals has recently received attention. Video display terminals produce both power-frequency fields and higher frequency fields ranging from about 50 Hz up to 50 kHz (Portier & Wolfe, 1998). Sandström *et al.* (1993) reported median magnetic fields at ELF as 0.21 μT and 0.03 μT for frequencies between 15 kHz and 35 kHz. The median electric fields measured in the same frequency ranges were 20 V/m and 1.5 V/m, respectively.

(vi) *Use of sewing machines*

Hansen *et al.* (2000) reported higher-than-background magnetic fields near industrial sewing machines, because of proximity to motors, with field strengths ranging from 0.32–11.1 μT at a position corresponding approximately to the sternum of the operator. The average exposure for six workers working a full work-shift in the garment industry ranged from 0.21–3.20 μT.

(*c*) *Transients*

Transients occur in electrical systems mainly as a result of switching loads or circuits on and off. They can be produced deliberately, as in circuit testing, or occur accidentally, caused by sudden changes in current load following a short-circuit or lightning strike. Such disturbances invariably have a much higher frequency content than that of the signal that is interrupted (Kaune *et al.*, 2000).

A number of devices have been designed to record electric power transients (Deadman *et al*., 1988; Héroux, 1991; Kaune *et al*., 2000). These devices differ primarily in the range of frequencies used to define a transient and in their storage capacities. Kaune *et al.* (2000) examined magnetic transients within the range of 2–200 kHz that had threshold peak intensity levels, measured using a dual channel recorder, of either 3.3 or 33 nT. Recordings were made for a minimum of 24 h in each of 156 homes distributed at six different locations in the USA. Although the recordings of the less intense 3.3-nT transients might have been contaminated somewhat by nearby television sets, this was not the case for the recordings of the 33-nT transients. It was found that transient activity in homes has a distinct diurnal pattern, generally following variations in power use. Evidence was also presented indicating that the occurrence of the larger, 33-nT magnetic transients is increased ($p = 0.01$) in homes with well-grounded metal plumbing that is also electrically connected to an external water system. In contrast, the increased transient activity in the homes tested was not related to wire code.

1.2 Instrumentation and computational methods of assessing electric and magnetic fields

1.2.1 *Instruments*

Measurements of electric and magnetic fields are used to characterize emissions from sources and exposure of persons or experimental subjects. The mechanisms that define internal doses of ELF electric and magnetic fields and relate them to biological effects are not precisely known (Portier & Wolfe, 1998) with the exception of the well-studied neurostimulatory effects of electric and magnetic fields (Bailey *et al*., 1997; Reilly, 1998). Therefore, it is important that investigators recognize the possible absence of a link between selected measured fields and a biological indicator of dose. The instrument best suited to the purpose of the investigation should be selected carefully. Investigators should evaluate the instrument and its proposed use before starting a study and calibrate it at appropriate intervals thereafter.

Early epidemiological and laboratory studies used simple survey instruments that displayed the maximum field measured along a single axis. More recent studies of magnetic fields have used meters that record the field along three orthogonal axes and report the resultant root-mean-square (rms) field as:

$$\text{Resultant} = \sqrt{(X^2 + Y^2 + Z^2)}$$

Survey meters are easy to use, portable and convenient for measuring field magnitudes over wide areas or in selected locations. Three-axis survey meters are capable of simple signal processing, such as computing the resultant field, storing multiple measurements in their memory or averaging measurements. It is important to note that the resultant field can be equal to, or up to 40% greater (for a circularly polarized field) than, the maximum field measured by a single-axis meter (IEEE, 1995a). Computer-based waveform capture measurement systems are designed to perform sophisticated signal processing and to record signals over periods ranging from a fraction of a second to several days. The instruments discussed here are those most commonly used for measuring fields in the environment or laboratory (Table 7). The measurement capabilities of selected instruments are summarized in Table 8. Less frequently used instruments designed for special purposes are described elsewhere (e.g. WHO, 1984, 1987). The operation of the electric and magnetic field meters recommended for use is described in IEEE (1995a) and IEC (1998).

Table 7. General characteristics of intruments

Meter type	Primary uses	Field parameters measured	Data-collection features	Cost	Ease of use	Data recording	Portability
Computer-based waveform measure-ment systems	Spot measurements	AC/DC field magnitude (x,y,z, resultant)	Full waveform capture	Very high	High-level technical understanding required	Digitized recording features	Less portable than typical meters
	Mapping	AC field magnitude at each frequency of interest (x,y,z axes, resultant)	Highest quantifi-cation content in data collection		The vast quantities of data collected are difficult to manage (approximately 50 kbytes for an average spot measurement vs. 10 bytes with a three-axis AC-field recording meter)		5-kg ‘portable’ system commercially available
	Long-term measurements	AC field polarization					
	Waveform capture	AC–DC orientation					
	Transient capture	Peak-to-peak					
Three-axis AC field recording root-mean-square meter	Personal exposure Spot measurements	AC field magnitude (x,y,z axes, resultant) in a bandwidth dependent upon model	Many have software for mapping capabilities if used with mapping wheel	Medium–high	Almost no instruction required for accurate resultant measurements	Recording features	Small, portable
	Mapping	Some models can provide harmonic content			More difficult to use for exploratory measurements (‘sniffing’) than single-axis meters because of delay between readouts		
	Long-term measurements						
	Exploratory measurements						

Table 7 (contd)

Meter type	Primary uses	Field parameters measured	Data-collection features	Cost	Ease of use	Data recording	Portability
Three-axis cumulative exposure meter with display	Personal exposure Spot measurements Exploratory measurements Long-term measurements for cumulative information	AC field magnitude (x,y,z axes, resultant) in a bandwidth dependent upon model	Most frequently used for personal exposure measurements	Medium	Almost no instruction required for accurate resultant measurements	Records accumulated data, rather than individual samples	Small, portable
Three-axis AC-field survey meter	Spot measurements	AC-field magnitude (x,y,z axes, resultant) in a bandwidth dependent upon model	Similar to three-axis recording meters, with recording capabilities	Medium	Almost no instruction required for accurate resultant measurement	No recording feature	Small, portable
	Exploratory measurements	Some models can provide total harmonic content			More difficult to use for exploratory measurements (‘sniffing’) than single-axis meters because of delay between readouts		
Single-axis AC-field survey meter	Exploratory measurements	AC field magnitude in one direction, in a bandwidth dependent upon model	Can be used to determine polarization	Low	Continuous readout provides easy source investigation	No recording feature	Small, portable
	Spot measurements	Some models can be switched from flat to linear response to provide rough data on presence of harmonics	Easy determination of direction of field Can be used with an audio attachment. For exploratory measurements		Maximum field must be ‘found’ by properly rotating the meter, or measuring in three orthogonal directions to calculate the resultant field		

AC, alternating current; DC, direct current
For further details and handling information, see IEC (1998).

Table 8. Characteristics of field meters

Model	Fields	Sensor	No. of axes	Frequency response (Hz)[a]	Maximum full-scale range (μT)	Output		Function	Comment
AMEX	B	C	1	–	12.5	TWA	AVG	P	
AMEX-3D	B	C	3	25 Hz–1.2 kHz	15	TWA	AVG	P	
EMDEX C	B, E	C, P	3,1	40–400 Hz	2550	D, DL	AVG	P	Built-in E field
EMDEX II	B	C	3	40–800 Hz	300	D, DL	RMS	P	Has harmonic capability
Positron	B, E, HF	C, P, F	3,1	50–60 Hz	50	D, DL	PEAK	P	Built-in E field
Monitor Ind.	B	C	1	40 Hz–1 kHz	250	A	RMS	S	
Multiwave	B	C, FG	3	0–10 kHz	500	D, DL	RMS	S	Waveform capture
Power frequency Meter MOD120	B, E	C, P	1	35–600 Hz	3000	A	AVG	S	
STAR[b]	B	C	3	60 Hz	51	D, DL	RMS	S	
MAG 01	B	FG	1	0–10 Hz	200	D	–	S	
IREQ	B	C	3	40 Hz–1 kHz	100	D, DL	RMS	S	
Field meter	B, E	D	1,1	25 Hz–10 MHz	–	–	–	S	Used by Hietanen & Jokela (1990)
BMM - 3000	B	C	3	5 Hz–2 kHz	2000	A	RMS	S	Frequency filters MPR/TC092 Band I testing
Sydkraft	B	C	1	50–60 Hz	20	D, DL	AVG	S	

Modified from Portier & Wolfe (1998)

E, electric; B, magnetic; HF, high frequency; C, coil, P (sensor), plate; F, conductive foam; FG, flux gate; D (sensor), active dipole; D (output), digital spot; A, analogue spot; DL, data logging; TWA, single readout of TWA; AVG, average; RMS, root-mean-square; P (function), personal monitor; S, survey

[a] Frequency response and maximum range refer only to the magnetic field measurement channel

[b] The specifications are for the original STAR meter that was produced only in limited quantities for non-commercial use. The commercial version of the instrument (Field StAR from Dexsil) has a range of 100 μT on each of three orthogonal axes.

(*a*) *Electric fields*

(i) *Survey meters*

The meters commonly used in occupational and environmental surveys of electric fields are small both for convenience and to minimize their effect on the electric field being measured. To measure the unperturbed field, the meter is suspended at the end of a long non-conductive rod or tripod to minimize interference with the measurement by the investigator. In an oscillating electric field, the current measured between two isolated conducting parts of the sensor is proportional to the field strength. The accuracy of the measurements obtained with these instruments is generally high, except under the following conditions:

- extremes of temperature and humidity;
- insufficient distance of the probe from the investigator;
- instability in meter position;
- loss of non-conductive properties of the supporting rod.

Electric fields can also be measured at fixed locations, e.g. under transmission lines or in laboratory exposure chambers by measuring the current collected by a flat conducting plate placed at ground level. For sinusoidal fields, the electric flux density can be calculated from the area of the plate (A), the permittivity of a vacuum (ε_0), the frequency (f) and the measured current induced in the plate (I_{rms}) in the expression below:

$$E = \frac{I_{rms}}{2\pi f \varepsilon_0 A}$$

Electric field meters can be calibrated by placing the probe in a uniform field produced between two large conducting plates for which the field strength can be easily calculated (IEEE, 1995a, b).

(ii) *Personal exposure meters for measuring electric fields*

Personal exposure meters are instruments for measuring the exposure of a person to electric fields in various environments, e.g. work, home and travel (see below for personal exposure meters for measuring magnetic fields). However, wearing a meter on the body perturbs the electric field being measured in unpredictable ways. Typically, where exposure to electric fields of large groups of subjects is being measured, a meter is placed in an armband, shirt pocket or belt pouch (Male *et al*., 1987; Bracken, 1993). Perturbation of the ambient field by the body precludes obtaining an absolute value of the field and, at best, the average value of such measurements reflects the relative level of exposure.

(*b*) *Magnetic fields*

(i) *Survey meters*

Magnetic fields can be measured with a survey meter, fixed location monitor or a wearable field meter. The simplest meter measures the voltage induced in a coil of wire. For a sinusoidally varying magnetic field, **B,** of frequency *f*, the voltage, V, induced in the coil is given by:

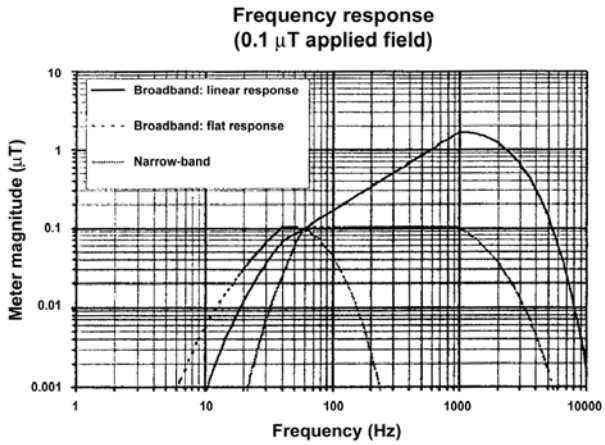
$$V = -2\pi f \mathbf{B}_0 A \cos\omega t$$

where *f* is the frequency of the field and $\omega = 2\pi f$, A is the area of the loop, and $\mathbf{B}_0$ is the component of **B** perpendicular to the loop.

The voltage induced by a given field increases with the addition of turns of wire or of a ferromagnetic core. To prevent interference from electric fields, the magnetic field probe must be shielded. If the meter is used for surveys or personal exposure measurements, frequencies lower than approximately 30 Hz must be filtered out to remove voltages induced in the probe by the motion of the meter in the earth's magnetic field.

The presence of higher frequencies, such as harmonics, can affect magnetic field measurements depending on the frequency response of the magnetic field meter. The frequency response of three different meters is illustrated in Figure 5 (modified from Johnson, 1998). These meters are calibrated so that a 60-Hz, 0.1-μT field reads as 0.1 μT on all three instruments. The narrow-band meter focuses on the 60-Hz magnetic field and greatly attenuates the sensitivity of the meter to higher and lower frequencies. The broadband meter provides an accurate measurement of the magnetic field across a wider frequency range because it has a flat frequency response between 40 Hz and 1000 Hz. The broadband meter with a linear response provides very different measurements in this range as the magnetic field reading is weighted by its frequency (Johnson, 1998).

Figure 5. Frequency response of linear broadband, flat broadband and narrow-band magnetic-field meters to a reference field of 0.1 μT



Modified from Johnson (1998)

Fluxgate magnetometers have adequate sensitivity for measuring magnetostatic fields in the range 0.1 μT–0.01 T. Above 100 μT, both AC and DC magnetic fields can be measured using a Hall effect sensor (IEEE, 1995b). The sensor is designed to measure the voltage across a thin strip of semiconducting material carrying a control current. The voltage change is directly related to the magnetic flux density of AC and DC magnetic fields (Agnew, 1992).

Early survey meters made average field readings and then extrapolated them to root-mean-square values by applying a calibration factor. These meters give erroneous readings when in the presence of harmonics and complex waveforms.

(ii) *Personal exposure meters for measuring magnetic fields*

Wearable meters for measuring magnetic fields have facilitated assessments of the personal exposure of individuals as they go about daily activities at home, school and work. A few instruments can also record electric-field measurements. The available personal exposure meters can integrate field readings in single or multiple data registers over the course of a measurement period. For a single-channel device, the result is a single value representing the integrated exposure over time in μT·h or (kV/m) h. Some meters classify and accumulate exposures into defined intensity 'bins'. Other personal exposure meters collect samples at fixed intervals and store the measurements in computer memory for subsequent downloading and analysis (see Table 9).

One of the most popular instruments used in occupational surveys and epidemiological studies is the electric and magnetic field digital exposure system (EMDEX). The EMDEX II data logger records the analogue output from three orthogonal coils or the computed resultant magnetic field. It can also record the electric field detected by a separate sensor. Different versions of the meter are used for environmental field ranges (0.01 μT–0.3 mT) and near high intensity sources (0.4 μT–12 mT) (data from the manufacturer, 2001).

Smaller, lighter versions of the EMDEX are available to collect time series records over longer time periods (EMDEX Lite) or to provide statistical descriptors — mean, standard deviation, minimum, maximum and accumulated time above specified thresholds — of accumulated measurements (EMDEX Mate). The AMEX (average magnetic exposure)-3D measures only the average magnetic field over time of use. IEC (1998) has provided detailed recommendations for the use of instruments in measuring personal exposure to magnetic fields.

(iii) *Frequency response*

The bandwidth of magnetic field meters is generally between 40 Hz and 1000 Hz. Further differentiation of field frequency within this range is not possible unless filtered to a narrow frequency band of 50 or 60 Hz. However, a data logger, the SPECLITE®, was employed in one study to record the magnetic field in 30 frequency bins within this range at 1-min intervals (Philips *et al.*, 1995).

Table 9. Commercially available instruments for measuring ELF magnetic fields[a]

Company, location	**Meter, field type**	**Frequency range**
AlphaLab Inc. Salt Lake City, Utah, USA	TriField Meter (3-axis **E**, **M** & **RF**)	50 Hz–3 GHz
Bartington Instruments Ltd Oxford, England	MAG-01 (1-axis **M**) MAG-03 (3-axis **M**)	DC–a few kHz 0 Hz–3000 Hz
Combinova AB Bromma, Sweden	MFM 10 (3-axis **M** recording) MFM 1020 (3-axis **E**, **M** recording) FD 1 (**E**, 3-axis **M** survey) FD 3 (3-axis **M** recording)	20 Hz–2000 Hz 5 Hz–400 kHz 20 Hz–2000 Hz 20 Hz–2000 Hz
Dexsil Corp. Hamden, Connecticut, USA	Field Star 1000 (3-axis **M** recording) Field Star 4000 (3-axis **M** recording) Magnum 310 (3-axis **M** survey)	not specified not specified 40 Hz–310 Hz
Electric Research Pittsburgh, Pennsylvania, USA	MultiWave® System II (**E**, **M** 3-axis, waveform)	0–3000 Hz
Enertech Consultants Campbell, California, USA	EMDEX SNAP (3-axis **M** survey) EMDEX PAL (3-axis **M** limited recording) EMDEX MATE (3-axis **M** limited recording) EMDEX LITE (3-axis **M** recording) EMDEX II (3-axis **E** & **M** recording) EMDEX WaveCorder (3-axis **M** waveform) EMDEX Transient Counter (3-axis **M**)	40 Hz–1000 Hz 40 Hz–1000 Hz 40 Hz–1000 Hz 10 Hz–1000 Hz 40 Hz–800 Hz 10 Hz–3000 Hz 2000 Hz–220 000 Hz
EnviroMentor AB Mölndal, Sweden	Field Finder Lite (1-axis **M** & **E**) Field Finder (3-axis **M** & 1-axis **E**) ML-1 (3-axis **M,** 3-dimensional presentation) BMM-3000 (3-axis **M**, analysis program)	15 Hz–1500 Hz 30 Hz–2000 Hz 30 Hz–2000 Hz 5 Hz–2000 Hz
Holaday Industries, Inc. Eden Prairie, Minnesota, USA	HI-3624 (**M**) HI-3624A (**M**) HI-3604 (**E, M**) HI-3627 (3-axis **M,** recorder output)	30 Hz–2000 Hz 5 Hz–2000 Hz 30 Hz–2000 Hz 5 Hz–2000 Hz
Magnetic Sciences International Acton, Massachusetts, USA	MSI-95 (1-axis **M**) MSI-90 (1-axis **M**) MSI-25 (1-axis **M**)	25 Hz–3000 Hz 18 Hz–3300 Hz 40 Hz–280 Hz
Physical Systems International Holmes Beach, Florida, USA	FieldMeter (1-axis **E**, **M**) FieldAnalyzer (1-axis **E**, 3-axis **M**, waveform)	16 Hz–5000 Hz 1 Hz–500 Hz
Sypris Test and Measurement Orlando, Florida, USA	4070 (1-axis **M**) 4080 (3-axis **M**) 4090 (3-axis **M**) 7030 (3-axis **M**)	40 Hz–200 Hz 40 Hz–600 Hz 50 Hz–300 Hz 10 Hz–50 000 Hz
Tech International Corp. Hallandale, Florida, USA	CellSensor (1-axis **M** & **RF**)	~50 Hz–~835 MHz

Table 9 (contd)

Company, location	**Meter, field type**	**Frequency range**
Technology Alternatives Corp. Miami, Florida, USA	ELF Digital Meter (**M**) ELF/VLF Combination Meter (**M**)	20 Hz–400 Hz 20 Hz–2000 Hz ELF; 10.000 Hz–200 000 Hz VLF
Walker LDJ Scientific, Inc. Worcester, Massachusetts, USA	ELF 45D (1-axis **M**) ELF 60D (1-axis **M**) ELF 90D (3-axis **M**) BBM-3D (3-axis **M**, ELF & VLF)	30 Hz–300 Hz 40 Hz–400 Hz 40 Hz–400 Hz 12 Hz–50 000 Hz

Source: Microwave News (2002) and industry sources
E, electric; **M**, magnetic (50 or 60 Hz); **RF**, radiofrequency; **ELF**, extremely low frequency; **VLF**, very low frequency
[a] Some instruments are suitable for measuring both magnetic and electric fields.

Specialized wave-capture instruments, such as the portable MultiWave system, can measure static and time-varying magnetic fields at frequencies of up to 3 kHz (Bowman & Methner, 2000). The EMDEX WaveCorder can also measure and record the waveform of magnetic fields for display and downloading.

In addition to measuring power-frequency fields, the Positron meter was designed to detect pulsed electric and magnetic fields or high-frequency transients associated with switching operations in the utility industry (Héroux, 1991). Only after its use in two epidemiology studies was it discovered that the readings of the commercial sensors were erratic and susceptible to interference from radiofrequency fields outside the bandwidth specification of the sensor. The interference by radio signals from hand-held walkie-talkies and other communication devices was recorded (Maruvada *et al.*, 2000).

The EMDEX Transient Counter, which has recently been developed, continuously measures changes in magnetic fields at frequencies between 2000 Hz and 220 000 Hz and reports the number of times that the change in amplitude exceeds thresholds of 5 nT and 50 nT (data from the manufacturer, 2001).

A list of some currently available instruments for measuring magnetic fields is given in Table 9.

1.2.2 *Computation methods*

For many sources, measurements are the most convenient way to characterize exposure to ELF electric and magnetic fields. However, unperturbed fields from sources such as power lines can also be easily characterized by calculations. Calculated electric field intensity and direction may differ from those that are measured because of the presence of conductive objects close to the source and/or near the location of interest.

The fields from power lines can be calculated accurately if the geometry of the conductors, the voltages and currents (amplitude and phase angle) in the conductors and

return paths are known. The currents flowing in the conductors of power lines are typically logged at substations and historical line-loading data may be available. However, in some cases, currents do not all return to utility facilities and may flow into the earth or into any conductor which is at earth potential, such as a neutral wire, telephone wire, shield wire or buried piping. Because the magnitude and location of the currents on these paths are not known, it is difficult or impossible to include them in computations.

The simplest calculations assume that the conductors are straight, parallel and located above, and parallel to, an infinite flat ground plane. Balanced currents are also typically assumed. Calculations of magnetic fields that do not include the contribution of small induced currents in the earth are accurate near power lines, but may not be so at distances of some hundreds of metres (Maddock, 1992). Very accurate calculations of the maximum, resultant and vector components of electric and magnetic fields are possible if the actual operating conditions at the time of interest are known, including the current flow and the height of conductors, which vary with ambient temperature and line loading.

A number of computer programs have been designed for the calculation of fields from power lines and substations. These incorporate useful features such as the calculation of fields from non-parallel conductors. While the computation of simple fields by such programs may be quite adequate for their intended purpose, it may be difficult for other investigators to verify the methods used to calculate exposures. Epidemiological studies that estimated the historical exposures of subjects to magnetic fields from power lines by calculations did not usually report using documented computer programs or publish the details of the computation algorithms, e.g. Olsen *et al.* (1993), Verkasalo *et al*. (1993, 1996), Feychting and Ahlbom (1994), Tynes and Haldorsen (1997) and UK Childhood Cancer Study Investigators (2000a). However, for exposure assessment in these studies, it is likely that the uncertainty in the historical loading on the power lines would contribute much more to the overall uncertainty in the calculated field than all of the other parameters combined (Jaffa *et al*., 2000).

Calculations are also useful for the calibration of electric and magnetic field meters (IEEE, 1995b) and in the design of animal and in-vitro exposure systems, e.g. Bassen *et al*. (1992), Kirschvink (1992), Mullins *et al*. (1993).

1.3 Exposure assessment

1.3.1 *External dosimetry*

(*a*) *Definition and metrics*

External dosimetry deals with characterization of static and ELF electric and magnetic fields that define exposure in epidemiological and experimental studies. For static fields, the field strength (or flux density) and direction unambiguously describe exposure conditions. As with other agents, the timing and duration of exposure are important parameters, but the situation is more complex in the case of ELF fields. The

difficulty arises, not from the lack of ability to specify complete and unique characteristics for any given field, but rather from the large number of parameters requiring evaluation, and, more importantly, the inability to identify the critical parameters for biological interactions.

Several exposure characteristics, also called metrics, that may be of biological significance have been identified (Morgan & Nair, 1992; Valberg, 1995). These include:

- intensity (strength) or the corresponding flux density, root mean square, average or peak value of the exposure field; or a function of the field strength such as field-squared;
- duration of exposure at a given intensity;
- time (e.g. daytime versus night-time);
- single versus repeated exposure;
- frequency spectrum of the field; single frequency, harmonic content, intermittency, transients;
- spatial field characteristics: orientation, polarization, spatial homogeneity (gradients);
- single field exposure, e.g. ELF magnetic versus combined electric and magnetic field components, and possibly their mutual orientation;
- simultaneous exposure to a static (including geomagnetic field) and ELF field, with a consideration of their mutual orientation;
- exposure to ELF fields in conjunction with other agents, e.g. chemicals.

The overall exposure of a biological system to ELF fields can be a function of the parameters described above (Valberg, 1995).

(*b*) *Laboratory exposure systems*

Laboratory exposure systems have the advantage that they can be designed to expose the subjects to fields of specific interest and the fields created are measurable and controllable. Laboratory exposure systems for studying the biological effects of electric and magnetic fields are readily classified as *in vivo* or *in vitro*. Most studies of exposure *in vivo* have been in animals; few have involved humans. In-vitro studies of exposure are conducted on isolated tissues or cultured cells of human or animal origin.

One reason for studying the effects of very strong fields is the expectation that internal dose is capable of being biologically scaled. For this reason, many laboratory experiments have been performed at field strengths much higher than those normally measured in residential and occupational settings. This approach is usually used on the assumption that the amplitude of biological effects increases with field strength up to the maxima set in exposure guidelines, and the physical limitations of the exposure system.

(i) *In-vivo exposure systems*

Many in-vivo studies have used magnetostatic fields (Tenforde, 1992; see also section 4). Both iron-core electromagnets and permanent magnets are routinely used in such studies. Although it is theoretically possible to obtain even larger DC magnetic

fields from iron-core devices (up to approximately 2 T), there is a limitation on the size of the active volume between the pole faces where the field is sufficiently uniform. Experimental studies of fields greater than 1.5 T are difficult because limited space is available for exposing biological systems to reasonably uniform magnetic fields.

The most commonly used apparatus for studying exposure to electric fields consists of parallel plates between which an alternating voltage (50 or 60 Hz, or other frequencies) is applied. Typically, the bottom plate is grounded. When appropriate dimensions of the plates are selected (i.e. a large area in comparison to the distance between the plates), a uniform field of reasonably large volume can be produced between the plates. The distribution of the electric-field strength within this volume can be calculated. The field becomes less uniform close to the plate edges.

A uniform field in an animal-exposure system can be significantly perturbed by two factors. An unavoidable but controllable perturbation is due to the presence of test animals and their cages. Much information is available on correct spacing of animals to ensure similar exposure for all test animals and to limit the mutual shielding of the animals (Kaune, 1981a; Creim *et al*., 1984). Animal cages, drinking bottles, food and bedding cause additional perturbations of the electric field (Kaune, 1981a). One of the most important causes of artefactual results in some studies is induction of currents in the nozzle of the drinking-water container. If the induced currents are sufficiently large, animals experience electric microshocks while drinking. Corrective measures have been developed to alleviate this problem (Free *et al*., 1981). Perturbation of the exposure field by nearby metallic objects is easy to prevent. The faulty design, construction and use of the electric-field-exposure facility can result in unreliable exposure over and above the limitations that normally apply to animal bioassays.

A magnetic field in an animal-exposure experiment is produced by current flowing through an arrangement of coils. The apparatus can vary from a simple set of two Helmholtz coils (preferably square or rectangular to fit with the geometry of cages), to an arrangement of four coils (Merritt *et al*., 1983), to more complicated coil systems (Stuchly *et al*., 1991; Kirschvink, 1992; Wilson *et al*., 1994; Caputa & Stuchly, 1996). The main objectives in designing apparatus for exposure to magnetic fields are (1) to ensure the maximal uniformity of the field within as much as possible of the volume encompassed by the coils, and (2) to minimize the stray fields outside the coils, so that sham-exposure apparatus can be placed in the same room. Square coils with four windings arranged according to the formulae of Merritt *et al*. (1983) best satisfy the field-uniformity requirement. Limiting the stray fields is a challenge, as shielding magnetic fields is much more complex than shielding electric fields. Non-magnetic metal shields only slightly reduce the field strength. Only properly designed multilayer-shielding enclosures made of high-permeability materials are effective. An alternative solution relies on partial field cancellation. Two systems of coils placed side by side or one above the other form a quadrupole system that effectively decreases the magnetic field outside the exposure system (Wilson *et al.*, 1994). An even greater reduction is obtained with a doubly compensating arrangement of coils. Four coils (each consisting

of four windings) are arranged side by side and up and down; coils placed diagonally are in the same direction as the field, and the neighbouring coils are in the opposite direction (Caputa & Stuchly, 1996).

Likely artefacts associated with magnetic-field-exposure systems include heating, vibrations and audible or high-frequency (non-audible to humans) noise. These factors can be minimized (although not entirely eliminated) with careful design and construction, which can be costly. The most economical and reliable way of overcoming these problems is through essentially identical design and construction of the field- and sham-exposure systems except for the current direction in bifilarly wound coils (Kirschvink, 1992; Caputa & Stuchly, 1996). This solution provides for the same heating of both the control and exposed systems. Vibration and noise are usually not exactly the same but are similar. To limit the vibration and noise, the coil windings should be restricted mechanically in their motion.

Another important feature of a properly designed magnetic-field system is shielding against the electric field produced by the coils. Depending on the coil shape, the number of turns in the coil and the diameter of the wire, a large voltage drop can occur between the ends of the coils. Shielding of the coils can eliminate interference from the electric field.

(ii) *In-vitro exposure systems*

Cell and tissue cultures can be exposed to the electric field produced between parallel plates in the same way that animals are exposed. In practice, this procedure is hardly ever used, because the electric fields in the in-vitro preparation produced this way are very weak, even for strong applied fields. For instance, an externally applied field of 10 kV/m at 60 Hz results in only a fraction of a volt per metre in the culture (Tobey *et al*., 1981; Lymangrover *et al*., 1983). Furthermore, the field strength is usually not uniform throughout the culture, unless the culture is thin and is placed perpendicular or parallel to the field. A practical solution involves the placement of appropriate electrodes in the cultures. Agar or other media bridges can be used to eliminate the problem of electrode contamination (McLeod *et al*., 1987). A comprehensive review of in-vitro exposure systems has recently been published (Misakian *et al*., 1993).

The shape and size of the electrodes determine the uniformity of the electric field and associated spatial variations of the current density. Either accurate modelling or measurements, or preferably both, should be performed to confirm that the desired exposure conditions are achieved. Additional potential problems associated with this type of exposure system are the heating of the medium and accompanying induced magnetic fields. Both of these factors can be evaluated (Misakian *et al*., 1993).

Coils similar to those used for animal studies can be used for in-vitro experiments (Misakian *et al*., 1993). The greatest uniformity is achieved along the axis within the volume enclosed in the solenoid. One great advantage of solenoids over Helmholtz coils is that the uniform region within the solenoid extends from the axis across the whole of the cross-sectional diameter.

In in-vitro studies, special attention should be paid to ambient levels of 50 or 60 Hz and to other magnetic fields. Magnetic flux densities from incubators unmodified for bioeffect studies may have background gradients of magnetic fields ranging from a few tenths of a microtesla to approximately 100 μT. Similarly, some other laboratory equipment with an electric motor might expose biological cells to high, but unaccounted for, magnetic flux densities. Specially designed in-vitro systems can avoid these problems. Exposure to magnetic fields that is unaccounted for or is at an incorrect level, as well as the critical influence of temperature and carbon dioxide concentration on some cell preparations, can lead to unreliable findings in laboratory experiments (Misakian *et al.*, 1993).

In some in-vitro studies, simultaneous exposure to alternating and static magnetic fields is used in a procedure intended to test the hypothesis of possible 'resonant' effects. Almost all the requirements for controlled exposure to the alternating field apply to the static field. Some precautions are not required in static field systems. For example, static systems have no vibrations (with the possible exception of on and off switching) so prevention of vibrations is unnecessary. In experiments involving static magnetic fields, the earth's magnetic field should be measured and controlled locally.

1.3.2 *Internal dosimetry modelling*

(*a*) *Definition for internal dosimetry*

At ELF, electric fields and magnetic fields can be considered to be uncoupled (Olsen, 1994). Therefore, internal dosimetry is also evaluated separately. For simultaneous exposure to both fields, internal measures can be obtained by superposition. Exposure to either electric or magnetic fields results in the induction of electric fields and associated current densities in tissue. The magnitudes and spatial patterns of these fields depend on the type of field (electric or magnetic), its characteristics (frequency, magnitude, orientation), and the size, shape and electrical properties of the exposed body (human, animal). Exposure to electric fields also results in an electric charge on the body surface.

The primary dosimetric measure is the induced electric field in tissue. The most frequently reported dosimetric measures are the average, root-mean-square and maximum induced electric field and current density values (Stuchly & Dawson, 2000). Additional measures include the 50th, 95th and 99th percentiles which indicate values not exceeded in a given volume of tissue, e.g. the 99th percentile indicates the dosimetric measure exceeded in 1% of a given tissue volume (Kavet *et al.*, 2001). The electric field in tissue is typically expressed in μV/m or mV/m and the current density in $\mu A/m^2$ or mA/m^2. Some safety guidelines (International Commission on Non-Ionizing Radiation Protection (ICNIRP), 1998) specify exposure limits measured as the current density averaged over 1 cm^2 of tissue perpendicular to the direction of the current.

The internal (induced) electric field **E** and conduction current density **J** are related through Ohm's law:

$$\mathbf{J} = \sigma\mathbf{E}$$

where the bold symbols denote vectors and σ is the bulk tissue conductivity which may depend on the orientation of the field in anisotropic tissues (e.g. muscle).

(*b*) *Electric-field dosimetry*

Early dosimetry models represented the human (or animal) body in a simplified way, as reviewed elsewhere (Stuchly & Dawson, 2000). During the past 10 years, several laboratories have developed sophisticated heterogeneous models of the human body (Gandhi & Chen, 1992; Zubal *et al*., 1994; Gandhi, 1995; Dawson *et al*., 1997; Dimbylow, 1997). These models partition the body into volumes of different conductivity. Typically, over 30 distinct organs and tissues are identified and represented by cubic cells (voxels) with 1–10-mm sides. Voxels are assigned a conductivity value based on the measured values reported by Gabriel *et al*. (1996). A model of the human body constructed from several geometrical bodies of revolution has also been used (Baraton *et al*., 1993; Hutzler *et al*., 1994).

Various methods have been used to compute induced electric fields in these high-resolution models. Because of the low frequency involved, exposures to electric and magnetic fields are considered separately and the induced vector fields are added, if needed. Exposure to electric fields is generally more difficult to compute than exposure to magnetic fields, since the human body significantly perturbs the electric field. Suitable numerical methods are limited by the highly heterogeneous electrical properties of the human body and the complex external and organ shapes. The methods that have been successfully used so far for high-resolution dosimetry are: the finite difference method in frequency domain and time domain, and the finite element method. The advantages and limitations of each method have been reviewed by Stuchly and Dawson (2000). Some of the methods and computer codes have been extensively verified by comparison with analytical solutions (Dawson & Stuchly, 1997).

Several numerical evaluations of the electric field and the current density induced in various organs and tissues have been performed (Dawson *et al*., 1998; Furse & Gandhi, 1998; Dimbylow, 2000; Hirata *et al*., 2001). Average organ (tissue) and maximum voxel values of the electric field and current density are typically reported. In the recent studies (Dimbylow, 2000; Hirata *et al.*, 2001), the maximum current density was averaged over 1 cm^2 for excitable tissues. The latter computation is clearly aimed at testing compliance with the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guideline (1998) and the commentary published thereafter (Matthes, 1998).

The induced electric fields computed in various laboratories are in reasonable agreement (Stuchly & Gandhi, 2000). As expected, smaller differences are observed between calculated electric fields than between calculated values for current density.

The observed differences can be explained by differences between the body models and the conductivity values allocated to different tissues.

The differences observed in the results of high-resolution models depend in part upon the conductivity values assumed (Dawson *et al.*, 1998). In general, the lower the induced electric fields (the higher the current density) the higher the conductivity of tissue. The exceptions are those parts of the body associated with concave curvature, e.g. the tissue surrounding the armpits, where the electric field is enhanced. For the whole body, the computed average values do not differ by more than 2% (Stuchly & Dawson, 2000).

The resolution of the model influences the accuracy with which the induced fields are evaluated in various organs. Organs that are small in any dimension are poorly represented by large voxels. The maximum induced electric field is higher for the finer resolution. The differences are typically of the order of 50–190% for voxels of 3.6-mm sides compared to 7.2-mm voxels (Stuchly & Dawson, 2000).

The highest induced fields are found in a body that is in contact with perfect ground through both feet. The average values for the organs or tissues of a 'grounded' body are about two or three times those for a body in free space (Dawson *et al.*, 1998), and intermediate values are obtained for various degrees of separation from the ground. This dependence on the contact with or separation from a perfect ground is in agreement with earlier experimental data (Deno & Zaffanella, 1982).

The main features of dosimetry for exposure of a person standing in an ELF electric field can be summarized as follows:

- The magnitudes of the electric fields in tissue are typically 10^{-5}–10^{-8} lower than the magnitude of the external field.
- For exposure to external fields from power lines, the predominant direction of the induced fields is also vertical.
- The largest fields in a human body are induced by a vertical electric field when the feet are in contact with a perfectly conducting ground plane.
- The weakest fields are induced in a body when it is in free space, i.e. infinitely far from the ground plane.
- The short-circuit current for a body in contact with perfect ground is determined by the size and shape of the body (including posture), rather than its tissue conductivity.

Table 10 summarizes the computed internal electric fields for a model of an adult body in a vertical field of 1 kV/m at 60 Hz (Kavet *et al.*, 2001), where the body (1.77 m in height and 76 kg in weight) makes contact with a perfectly conducting ground with both feet. Table 11 summarizes computed internal electric fields for a model of a five-year-old child (1.10 m in height and 18.7 kg in weight) (Hirata *et al.*, 2001). Selected conductivity values are given in Table 2 of the General Introduction. Dawson *et al.* (2001) demonstrated that the voxel maximum values are significantly overestimated, and the 99th percentiles are therefore more representative.

Table 10. Calculated electric fields (mV/m) in a vertical uniform electric field (60 Hz, 1 kV/m) induced in a model of a grounded adult human body[a]

Tissue/organ	E_{avg}	$E_{99\ percentile}$	E_{max}
Blood	1.4	8.9	24
Bone marrow	3.6	34	41
Brain	0.86	2.0	3.7
Cerebrospinal fluid	0.35	1.0	1.6
Heart	1.4	2.8	3.6
Kidneys	1.4	3.1	4.5
Lungs	1.4	2.4	3.6
Muscle	1.6	10	32
Prostate	1.7	2.8	3.1
Spleen	1.8	2.6	3.2
Testes	0.48	1.2	1.6

Modified from Kavet *et al*. (2001)

[a] Corresponding current densities can be computed from tissue conductivity values (see Table 2, General Introduction)

Table 11. Calculated electric fields (mV/m) in a vertical uniform electric field (60 Hz, 1 kV/m), induced in a model of the grounded body of a child

Tissue/organ	E_{avg}	$E_{99\ percentile}$	E_{max}
Blood	1.5	9.2	18
Bone marrow	3.7	35	42
Brain	0.7	1.6	3.1
Cerebrospinal fluid	0.28	0.87	1.4
Heart	1.6	3.1	3.7
Lungs	1.6	2.6	3.7
Muscle	1.7	10	31

Modified from Hirata *et al*. (2001)

Exposure in occupational situations, e.g. in a substation, where a person is close to a conductor at high potential, induces greater electric fields in certain organs (e.g. brain) than would be predicted from the measured exposure field 1.5 m above ground (Potter *et al*., 2000). This is to be expected, since the external field increases above the ground.

(*c*) *Magnetic-field dosimetry*

Early dosimetry models represented the body as a circular loop corresponding to a given body contour to determine the induced electric field or current density based on Faraday's law:

$$| \mathbf{J} | = \pi f \sigma r | \mathbf{B} |$$

where *f* is the frequency, r is the loop radius and **B** is the magnetic flux density vector perpendicular to the current loop. Similarly, ellipsoidal loops have been used to fit the body shape better.

More realistic models of the human body have been analysed by the numerical impedance method (Gandhi & De Ford, 1988; Gandhi & Chen, 1992; Gandhi *et al*., 2001) and the scalar potential finite difference technique (Dawson & Stuchly, 1998; Dimbylow, 1998). The dosimetry data available for magnetic fields are more extensive than those for electric fields. The effects of tissue properties in general (and specifically muscle anisotropy), field orientation with respect to the body and, to a certain extent, body anatomy have been investigated (Dawson *et al*., 1997; Dawson & Stuchly, 1998; Dimbylow, 1998). In the past, the largest loop of current fitted within a body part, e.g. head or heart, was often used to calculate the maximum current density in that body part. This is now known to underestimate the maximum induced field and the current densities (Stuchly & Dawson, 2000)

The main features of dosimetry for exposure to uniform ELF magnetic fields can be summarized as follows:

- The induced electric fields depend on the orientation of the magnetic field with respect to the body.
- For most organs and tissues, the magnetic field orientation perpendicular to the torso (front-to-back) gives maximum induced quantities.
- For the brain, cerebrospinal fluid, blood, heart, bladder, eyes and spinal cord, the strongest induced electric fields are produced by a magnetic field directed towards the side of the body.
- Magnetic fields oriented along the vertical body axis induce the weakest electric fields.
- Stronger electric fields are induced in bodies of larger size.

Table 12 lists the electric fields induced in certain organs and tissues by a 60-Hz, 1-μT magnetic field oriented front-to-back (Dawson *et al*., 1997; Dawson & Stuchly, 1998; Kavet *et al*., 2001).

The exposure of humans to relatively high magnetic flux densities occurs most often in occupational settings. Numerical modelling has been applied mostly to workers exposed to high-voltage power lines (Baraton & Hutzler, 1995, Stuchly & Zhao, 1996; Dawson *et al*., 1999a,b,c). In these cases, current-carrying conductors can be represented as infinite straight-line sources. However, some of the exposure occurs in more complex scenarios, two of which have been analysed, and a more realistic representation of the source conductors based on finite line segments has been used

(Stuchly & Dawson, 2000). Table 13 lists calculated electric fields for the two representative exposure scenarios illustrated in Figure 6 (Stuchly & Dawson, 2000).

Table 12. Calculated electric fields (μV/m) in a uniform magnetic field (60 Hz, 1 μT) oriented front-to-back induced in a model of an adult human

Tissue/organ	E_{avg}	$E_{99\ percentile}$	E_{max}
Blood	6.9	23	83
Bone marrow	16	93	154
Brain	11	31	74
Cerebrospinal fluid	5.2	17	25
Heart	14	38	49
Kidneys	25	53	71
Lungs	21	49	86
Muscle	15	51	147
Prostate	17	36	52
Spleen	41	72	92
Testes	15	41	73

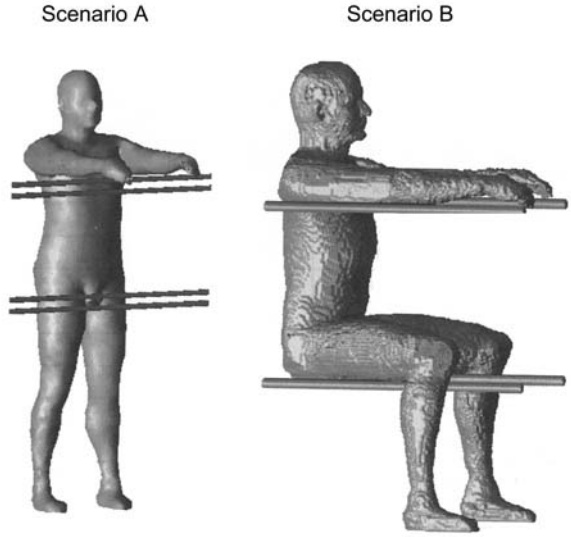
Modified from Kavet *et al*. (2001)

Table 13. Calculated electric fields (mV/m) induced in a model of an adult human for the occupational exposure scenarios shown in Figure 6 (total current in conductors, 1000 A)

Tissue/organ	Scenario A		Scenario B	
	E_{max}	E_{rms}	E_{max}	E_{rms}
Blood	20	3.7	15	2.4
Bone	90	11	58	7.2
Brain	22	4.6	28	5.9
Cerebrospinal fluid	9.2	2.3	14	3.7
Heart	27	11	9.0	3.2
Kidneys	22	7.9	2.8	0.9
Lungs	31	10	9.9	2.9
Muscle	59	6.9	33	5.5
Prostate	5.5	1.9	2.6	1.2
Testes	18	5.5	2.7	1.2

Modified from Stuchly & Dawson (2000)

Figure 6. Body positions in two occupational exposure scenarios



From Stuchly & Dawson (2000)
The current in each conductor is 250 A for a total of 1000 A in four conductors.

(*d*) *Contact-current dosimetry*

Contact currents produce electric fields in tissue similar to those induced by external electric and magnetic fields. Contact currents are encountered in a dwelling or work-place when a person touches conductive surfaces at different potentials and completes a path for current flow through the body. The current pathway is usually from hand-to-hand and/or from a hand to one or both feet. Sources of contact current may include an appliance chassis or household fixture that, because of typical residential wiring practices, carries a small potential above a ground. Other sources of contact current are conductive objects situated in an electric field, such as a vehicle parked under a power line. The importance of contact currents has been suggested by Kavet *et al.* (2000). Recently, electric fields have been computed in a model of a child with electrodes on hands and feet simulating contact current (Dawson *et al.*, 2001). The most common source of exposure to contact current is touching an ungrounded object while both feet are grounded. The electric fields calculated to be induced in the bone marrow of the hand and arm of a child for a 1-μA contact current are shown in Table 14. Electric fields above 1 mV/m can be produced in the bone marrow of a child from a low contact current of 1 μA. In residential settings such a current could result from an open-circuit voltage of only 100 mV, which is not uncommon. A total resistance of 5–10 kΩ is representative (Kavet *et al*., 2000). Provided that there is good contact to the ground, only 5–10 mV is needed to produce a current of 1–2 μA. Contact current with vehicles in an electric field

Table 14. Calculated electric field (mV/m) induced by a contact current of 60 Hz, 1 μA, in voxels of bone marrow of a child

Body part	E_{avg}	$E_{99\ percentile}$
Lower arm	5.1	14.9
Upper arm	0.9	1.4
Whole body	0.4	3.3

Modified from Dawson *et al.* (2001)

(e.g. under high-voltage power lines) typically ranges from 0.1 mA per 1 kV/m for a car to 0.6 mA per 1 kV/m for a large truck (Deno & Zaffanella, 1982).

(*e*) *Biophysical relevance of induced fields*

The lowest electric field in tissue to be associated with well-documented biological effects (not necessarily harmful) has been estimated as 1 mV/m (Portier & Wolfe, 1998). It is interesting to compare the different exposure conditions that produce an internal field of this magnitude. Table 15 shows the average exposure to electric and magnetic fields required to induce a field of 1 mV/m in selected tissues (Stuchly & Dawson, 2000). Although the mechanisms for biological effects of fields at 1 mV/m are unclear, it is, nevertheless, interesting to compare the electric fields induced in humans by exposure to residential magnetic fields, electric fields and contact currents. Table 16 shows that the electric field induced in a model of a child's bone marrow (i.e. the tissue involved in leukaemia) is 10 times greater for the exposure to a contact current than for exposure to either the maximum electric or magnetic field encountered in a dwelling (Kavet *et al.*, 2000).

(*f*) *Microscopic dosimetry*

Macroscopic dosimetry that describes induced electric fields in various organs and tissues can be extended to more spatially refined models of subcellular structures to predict and understand biophysical interactions. The simplest cellular model for considering linear systems requires evaluation of induced fields in various parts of a cell. Such models, for instance, have been developed to understand neural stimulation (Plonsey & Barr, 1988; Basser & Roth, 1991; Reilly, 1992; Malmivuo & Plonsey, 1995). Computations are available as a function of the applied electric field and its frequency. Because cell membranes have high resistivity and capacitance (nearly constant for all mammalian cells and equal to 0.5–1 μF/cm^2) (Reilly, 1992), at sufficiently low frequencies, high fields are produced at the two poles of the membrane. The field is nearly zero inside the cell, as long as the frequency of the applied field is below the membrane relaxation frequency (~ 1 MHz) (Foster & Schwan, 1995). The total

Table 15. Calculated electric (grounded model) or magnetic field (front to back) source levels needed to induce average (E_{avg}) and maximum (E_{max}) electric fields of 1 mV/m

Organ	Electric field exposure		Magnetic field exposure	
	E_{avg} = 1 mV/m	E_{max} = 1 mV/m	E_{avg} = 1 mV/m	E_{max} = 1 mV/m
Blood	0.72 kV/m	61 V/m	115 µT	15 µT
Bone	0.31 kV/m	22 V/m	46 µT	6.0 µT
Brain	1.2 kV/m	355 V/m	87 µT	26 µT
Cerebrospinal fluid	3.3 kV/m	901 V/m	233 µT	52 µT
Heart	0.93 kV/m	457 V/m	56 µT	20 µT
Kidneys	0.97 kV/m	412 V/m	43 µT	18 µT
Liver	0.79 kV/m	372 V/m	38 µT	11 µT
Lungs	0.99 kV/m	435 V/m	46 µT	14 µT
Muscle	0.76 kV/m	43 V/m	57 µT	6.9 µT
Prostate	0.68 kV/m	442 V/m	58 µT	28 µT
Testes	1.8 kV/m	769 V/m	53 µT	20 µT
Whole body	0.59 kV/m	21 V/m	49 µT	1.3 µT

Modified from Stuchly & Dawson (2000)

Table 16. Calculated average electric field (mV/m) induced by an electric field, magnetic field and contact current in child's bone marrow (model)

Exposure	Scenario	Intensity	Electric field (mV/m)
Magnetic field	Uniform, horizontal and frontal exposure	10 µT	0.2
Electric field	Uniform, vertical grounded	100 V/m	0.3
Contact current	Current injection into shoulders	18 µA	3.5

Modified from Kavet *et al*. (2000)

membrane resistance and capacitance define this frequency; thus, it depends on the cell size (total membrane surface). The larger the cell, the higher the induced membrane potential for the same applied field, but the larger the cell, the lower the membrane relaxation frequency.

Gap junctions connect many cells. A gap junction is an aqueous pore or channel through which neighbouring cell membranes are connected. Thus, cells can exchange ions, for example, providing local intercellular communication (Holder *et al*., 1993). In gap-junction-connected cells there is electrical coupling between the cytoplasm of adjoining cells and such systems have previously been modelled as leaky cables (Cooper, 1984). Simplified models have also been used, in which a group of gap-junction-connected cells is represented by a large cell of the same size (Polk, 1992).

Using such models, relatively large membrane potentials have been estimated, even for applied fields of only moderate intensity. A numerical analysis has been performed to compute membrane potentials in more realistic multiple-cell models (Fear & Stuchly, 1998). Simulations have indicated that simplified models such as a single cell or leaky-cable can be used only in some specific situations. Even when these models are appropriate, equivalent cells must be constructed, in which the cytoplasm properties are modified to account for the properties of gap-junctions. These models are reasonably accurate for very small assemblies of cells of certain shapes exposed at very low frequencies. As the size of the cell-assembly increases, the membrane potential, even at static fields, does not increase linearly with dimensions as it does for very short elongated assemblies. There is also a limit to the membrane potential for assemblies of other shapes.

From this linear model of gap-connected cells, it can be concluded that, at 50 or 60 Hz, an induced membrane potential of 0.1 mV is not attained in any organ or tissue of the human body exposed to a uniform magnetic flux density of up to 1 mT or to an electric field of 10 kV/m or less (Fear & Stuchly, 1998). These external field levels are much higher than those that elicit 1 mV/m in the bone marrow.

1.4 Biophysical mechanisms

Beyond the well-established mechanisms of interaction described above, such as the induction of currents from time-varying magnetic fields, a number of hypotheses have been advanced to explain ELF and static field interactions. These include radical-pair mechanisms; charge-to-mass signature; biogenic magnetite; etc.

1.4.1 *Induced currents*

The role of induced currents has been discussed by Adair (1991) who argued that because currents induced by ambient-level magnetic fields are comparable to, or smaller than, those resulting from thermal fluctuations, they must have little physiological significance. This argument is based on calculations of the thermal (or ‘kT’) noise developed in the cell membrane. The four major sources of electrical noise in biological membranes are:

— Johnson–Nyquist thermally-generated electrical noise;
— 1/f noise produced by ion current through membrane channels;
— ‘shot’ noise resulting from the discrete nature of ionic charges; and
— endogenous fields produced by electrically active organs such as the heart, muscles and the nervous system (Tenforde, 1995).

However, it must be remembered that the electrical characteristics of the membrane are different from those of the other regions of the cell. Taking this into consideration, conclusions have been reached concerning the potential effects of weak ELF magnetic fields. For example, Adair (1991) calculated that the theoretical threshold sensitivity

for biological effectiveness due to Faraday induction by ELF magnetic fields was much larger. This threshold is much higher than those reported from a variety of laboratory experiments (Fitzsimmons *et al.*, 1995; Jenrow *et al*., 1996; Harland & Liburdy, 1997; Zhadin *et al.*, 1999; Blackman *et al*., 2001). If some of these experimental results are correct, the discrepancy between theoretical and experimental results indicates that the thermal-noise arguments have to be reconsidered. Indeed, low thresholds of 4 mV/m and 10 mV/m were calculated by Polk (1993) and Tenforde (1993), respectively, based on a redistribution of charges in the counterion layer rather than on changes in trans-membrane potential. Amplification due to the electric coupling of large arrays of cells must also be taken into account in the estimation of threshold values.

1.4.2 *Radical-pair mechanism*

Increasing attention is being paid to the possibility that static and ELF magnetic fields may affect enzymatic processes that involve radical pairs (radical-pair mechanism). The radical-pair mechanism is a well established physical mechanism for describing how applied magnetic flux densities as low as 0.1–1 mT can affect chemical or biochemical reactions nonthermally (Walleczek, 1995). The simplified radical-pair mechanism can be summarized as follows: according to Pauli's exclusion principle, two valence electrons of the same orbital differ in their quantum spin number and a pair can be represented with one electron having the spin up (↑) and the other a spin down (↓). When a molecular bond is broken, a pair of free radicals is produced in the so-called singlet state (↑↓) which can either recombine to the original molecule or separate into two free radicals. However, if the relative orientation of the spins is altered (inter-conversion from singlet to triplet), the kinetics of recombination are modified. Three types of process can change the orientation of the spins:

— hyperfine coupling (linked to the magnetic environment of the pair);
— differences in Larmor precession rates ('Δg' mechanism); and
— crossing from one energy level to another.

The first process, which corresponds to a decrease of the rate of the interconversion with increasing field strength, is the most likely to occur at low field-strength. Since the lifetime of the radical pair (nano- to microseconds) is much shorter than the period of the ELF signal (~ 20 ms), the ELF magnetic field can be considered as static when considering processes consisting of a single elementary chemical reaction. However, in biochemical systems involving enzymes, in which sequences of elementary reactions can lead to oscillations of concentrations of intermediate species occurring at ELFs, the external field could, in principle, couple to the system and have an effect even at low field-strength (Walleczek, 1995; Eichwald & Walleczek, 1997), possibly in the μT range, though arguments have been advanced that this could not occur at 5 μT (Adair, 1999). Experimental evidence for the radical-pair mechanism in biological processes at field strengths below 500 μT is still lacking (Brocklehurst & McLauchlan, 1996).

1.4.3 *Effects related to the charge-to-mass ratio of ions*

The results of several experimental studies suggest that consideration of some ELF magnetic field interactions requires that the static magnetic field be taken into account as well. The ion cyclotron resonance (ICR) model (Liboff, 1985) proposes that ion transfer through cell membranes is affected by cyclotron resonance when an alternating electric or magnetic field is superimposed on a static magnetic field, e.g. the geomagnetic field. It is based on the fact that the cyclotron resonance frequency of several physiologically important ions like Na^+, K^+, Mg^{2+} and Ca^{2+} falls into the ELF range. For example, for Mg^{2+} the resonance frequency would be 61.5 kHz in a static magnetic field of 50 μT, as can be calculated from the formula below (Liboff, 1985; Polk, 1995):

$$\omega_c = 2\,\pi f_c = \frac{q\,B_{DC}}{m}$$

where ω_c is the angular frequency of the alternating magnetic field, B_{DC} is the intensity of the static field, and q/m is the ionic charge-to-mass ratio. Despite the many reports (Thomas *et al.*, 1986; Rozek *et al.*, 1987; Smith *et al.*, 1987; Ross, 1990; Lerchl *et al.*, 1991; Liboff *et al.*, 1993; Smith *et al.*, 1993; Deibert *et al.*, 1994; Jenrow *et al.*, 1995; Zhadin *et al.*, 1999) that have indicated that such combinations of fields are effective in altering biological responses, there is no definitive experimental evidence and other authors have failed to replicate these effects (e.g. Parkinson & Hanks, 1989; Liboff & Parkinson, 1991; Parkinson & Sulik, 1992; Coulton & Barker, 1993).

Most importantly, there is no accepted explanation at either the microscopic or molecular level of how such field combinations could be effective. Therefore, this unique signature must, at present, be regarded as tentative and purely empirical in nature. There is some experimental evidence (Smith *et al.*, 1987) to indicate that higher frequency harmonics are also effective, following the allowed harmonic relation $f_n = (2n + 1)\,f_o$, n = 0, 1, 2, 3, …. The same authors also observed that, if all other parameters remain the same, small changes in B_{DC} (intensity of the static field) could shift the charge-to-mass ratio given above from one ionic species to another, with a totally different resultant change in the expected biological response. The implication is that, for one specific value of B_{AC} (intensity of the alternating field), there may be markedly contrasting biological outcomes if exposure to ELF fields occurs in different static fields. The geomagnetic field varies substantially over the earth's surface, and from place to place within the same building due to local perturbations. If interaction hypotheses based upon the ion charge-to-mass ratios were valid and furthermore were a cause of cancer, then it might be difficult for epidemiological studies to capture associations with exposure to ELF magnetic fields (Smith *et al.*, 1987).

From a theoretical model, Lednev (1991) suggested that the cyclotron resonance frequency appears in the transition probability of an excited state of a charged oscillator (e.g. Ca^{2+}) located in one of the binding sites of a protein. This parametric resonance

mechanism makes use of Zeeman splitting of the energy levels in a magnetic field. In addition to the ionic charge-to-mass ratio and the static field intensity, which are both well-defined experimental parameters, the transition probability p(B) is also dependent on B_{AC}, a feature that was not considered in the original hypothesis (Liboff, 1985).

The field-dependent part of the parametric resonance mechanism transition probability is to a first approximation:

$$p(B) = (-1)^n K J_n (nB_{AC}/B_{DC})$$

where K is a constant and J_n is the nth order Bessel function with argument (nB_{AC}/B_{DC}).

An alternative theoretical formulation, called the ion parametric resonance model (Blanchard & Blackman, 1994) is very similar to the parametric resonance mechanism model, except that it is not related to calcium-binding, but rather to enzyme activation. In the ion parametric resonance model, the transition probability becomes:

$$p(B) = (-1)^n K J_n (2nB_{AC}/B_{DC})$$

Exposure 'windows' are predicted in both models; the intensities at which these windows occur are entirely dependent on the respective arguments of the two Bessel functions. See section 4.3 for a description of experimental data in support of this formulation. By contrast, Adair (1992, 1998) gave reasons as to why these proposed mechanisms would not be expected to produce biological effects.

Other theoretical attempts to explain the experimental results have been made by Binhi (2000), using quantum mechanics to estimate the dissociation probability of an ion from a protein, and by Zhadin (1998), who hypothesized magnetically induced changes in the thermal energy distribution.

The hypothesis discussed above may explain the frequency 'windows' previously reported (Bawin & Adey, 1976; Blackman *et al*., 1985). If so, the exposure conditions related to cyclotron resonance may have to be considered in a discussion of exposure to electric and magnetic fields taking into account the role of the local geomagnetic field.

1.4.4 *Biogenic magnetite*

Following the original discovery by Blakemore (1975) that certain bacteria use iron-rich intracytoplasmic inclusions for orientational purposes, such domain-sized magnetite (Fe_3O_4) particles have been found in other biological systems, notably the human brain (Kirschvink *et al*., 1992). Kirschvink suggested that weak ELF magnetic fields coupling to biogenic magnetite might be capable of producing coherent biological signals. However, the number of magnetite crystals is exceeded by that of neurons by a factor of about 10 (Malmivuo & Plonsey, 1995) and, moreover, no experimental evidence exists to support this hypothesis. Based on a mathematical model, Adair (1993) has estimated that a 60-Hz magnetic field weaker than 5 μT could not generate a sufficiently large signal to be detectable in a biological system by interaction with magnetite. According to Polk (1994), reported experimental results

indicate effects in mammals of 50-Hz fields at the 1-μT level. Rather strong static magnetic fields are required to affect the orientation behaviour of honey bees, which depends, in part, upon the influence of the geomagnetic field on magnetite in the bee's abdomen (Kirschvink *et al.*, 1997).

1.4.5 *Other mechanisms*

Electric fields can increase the deposition of charged airborne particles on surfaces. It has been suggested that this well-known phenomenon could lead to increased exposure of the skin or respiratory tract to ambient pollutants close to high-voltage AC power lines (Henshaw *et al*., 1996; Fews *et al*., 1999a). It is also known that the high-voltage power-lines emit corona ions, which can affect the ambient distribution of electrical charges in the air (Fews & Henshaw, 2000). Fews *et al*. (1999b) have suggested that this could enhance the deposition of airborne particles in the lung. The relevance of these suggestions to health has not been established (Jeffers, 1996; Stather *et al*., 1996; Jeffers, 1999; Swanson & Jeffers, 1999; Fews & Henshaw, 2000; Swanson & Jeffers, 2000).

2. Studies of Cancer in Humans

2.1 Exposure assessment in epidemiological studies

2.1.1 *Considerations in assessment of exposure to electric and magnetic fields relevant to epidemiology*

Electric and magnetic fields are complex and many different parameters are necessary to characterize them completely. These parameters are discussed more fully in section 1. In general, they include transients, harmonic content, resonance conditions, peak values and time above thresholds, as well as average levels. It is not known which of these parameters or what combination of parameters, if any, are relevant for carcinogenesis. If there were a known biophysical mechanism of interaction for carcinogenesis, it would be possible to identify the critical parameters of exposure, including relevant timing of exposure. However, in the absence of a generally accepted mechanism for carcinogenesis, most exposure assessments in epidemiological studies are based on a time-weighted average of the field, a measure that is also related to many other characteristics of the fields (Zaffanella & Kalton, 1998).

Exposure to electric and magnetic fields and approaches for exposure assessment have been described in detail in section 1. Some of the characteristics of exposure to electric and magnetic fields which make exposure assessment for the purposes of epidemiological studies particularly difficult are listed below:

- *Prevalence of exposure*. Everyone in the population is exposed to some degree to ELF electric and magnetic fields and therefore exposure assessment has to separate the more from the less exposed individuals, as opposed to the easier task of separating individuals who are exposed from those who are not.
- *Inability of subjects to identify exposure.* Exposure to electric and magnetic fields, whilst ubiquitous, is neither detectable by the exposed person nor memorable, and hence epidemiological studies cannot rely solely on questionnaire data to characterize past exposures adequately.
- *Lack of clear contrast between 'high' and 'low' exposure*. The difference between the electric and magnetic fields to which 'highly exposed' and 'less highly exposed' individuals in a population are subjected is not great. The typical average magnetic fields in homes appear to be about 0.05–0.1 μT. Pooled analyses of childhood leukaemia and magnetic fields, such as that by Ahlbom

et al. (2000), have used ≥ 0.4 μT as a high-exposure category. Therefore, an exposure assessment method has to separate reliably exposures which may differ by factors of only 2 or 4. Even in most of the occupational settings considered to entail 'high exposures' the average fields measured are only one order of magnitude higher than those measured in residential settings (Kheifets *et al.*, 1995).

- *Variability of exposure over time*: *short-term*. Fields (particularly magnetic fields) vary over time-scales of seconds or longer. Assessing a person's exposure over any period involves using a single summary figure for a highly variable quantity.
- *Variability of exposure over time: long-term*. Fields are also likely to vary over time-scales of seasons and years. With the exception of historical data on loads carried by high-voltage power lines, data on such variation are rare. Therefore, when a person's exposure at some period in the past is assessed from data collected later, an assumption has to be made. The usual assumption is that the exposure has not changed. Some authors (e.g. Jackson, 1992; Petridou *et al*., 1993; Swanson, 1996) have estimated the variations of exposure over time from available data, for example, on electricity consumption. These apply to population averages and are unlikely to be accurate for individuals.
- *Variability of exposure over space*. Magnetic fields vary over the volume of, for example, a building so that, as people move around, they may experience fields of varying intensity. Personal exposure monitoring captures this, but other assessment methods generally do not.

People accumulate exposure to fields in different settings, such as at home, at school, at work, while travelling and outdoors, and there can be great variability of fields between these environments. Current understanding of the contributions to exposure from different sources and in different settings is limited. Most studies make exposure assessments within a single environment, typically at home for residential studies and at work for occupational studies. Some recent studies have included measures of exposure from more than one setting (e.g. Feychting *et al*., 1997; UK Childhood Cancer Study Investigators, 1999; Forssén, 2000).

In epidemiological studies, the distribution of exposures in a population has consequences for the statistical power of the study. Most populations are characterized by an approximately log-normal distribution with a heavy preponderance of low-level exposure and much less high-level exposure. Pilot studies of exposure distribution are important for developing effective study designs.

2.1.2 *Assessing residential exposure to magnetic fields*

(*a*) *Methods not involving measurement*

(i) *Distance*

The simplest possible way of assessing exposure is to record proximity to a facility (such as a power line or a substation) which is likely to be a source of field. This does provide a very crude measure of exposure to both electric and magnetic fields from that source, but takes no account of other sources or of how the fields vary with distance from the source (which is different for different sources). Distances reported by study subjects rather than measured by the investigators tend to be unreliable.

(ii) *Wire code*

Wire coding is a non-intrusive method of classifying dwellings on the basis of their distance from visible electrical installations and the characteristics of these installations. This method does not take account of exposure from sources within the home.

Wertheimer and Leeper (1979) devised a simple set of rules to classify residences with respect to their potential for having a higher than usual exposure to magnetic fields. Their assumptions were simple:

- the field strength decreases with distance from the source;
- current flowing in power lines decreases at every pole from which ‘service drop’ wires deliver power to houses;
- if both thick and thin conductors are used for lines carrying power at a given voltage, and more than one conductor is present, it is reasonable to assume that more and thicker conductors are required to carry greater currents; and
- when lines are buried in a conduit or a trench, their contribution to exposure can be neglected. This is because buried cables are placed close together and the fields produced by currents flowing from and back to the source cancel each other much more effectively than when they are spaced apart on a cross beam on a pole.

Wertheimer and Leeper (1979) used these four criteria to define two and later four (Wertheimer & Leeper, 1982) then five (Savitz *et al.*, 1988) classes of home: VHCC (very high current configuration), OHCC (ordinary high current configuration), OLCC (ordinary low current configuration), VLCC (very low current configuration) and UG (underground, i.e. buried). The houses with the higher classifications were assumed to have stronger background fields than those with lower classifications.

Wire coding, in the original form developed by Wertheimer and Leeper, has been used in a number of studies. Although some relationship between measured magnetic fields and the wire-coding classification is seen in all studies (see for example Table 17 for studies of childhood leukaemia), wiring codes generally misclassify many homes although they do differentiate between high-field homes and others (Kheifets *et al.*, 1997a).

Table 17. Typical mean values of time-weighted average magnetic fields (μT) — and percentage of houses > 0.2 μT — associated with wire-code exposure classes from childhood leukaemia studies

Reference, country	Classification	Underground (UG)	Very low (VLCC)	Low (LCC)	High (HCC)	Very high (VHCC)
Savitz *et al.* (1988)[a]	No. of observations	133	27	174	88	12
	mean (μT)	0.05	0.05	0.07	0.12	0.21
USA	% > 0.2 μT	3	0	6	21	60
Tarone *et al.* (1998)[b]	No. of homes	150	221	262	170	55
	mean (μT)	0.06	0.08	0.12	0.14	0.2
USA	% > 0.2 μT	3	6	15	20	40
McBride *et al.* (1999)[c]	No. of residences	127	137	131	164	43
	mean (μT)	0.09	0.08	0.11	0.17	0.26
Canada						
Green *et al.* (1999a)[d]	No. of measurements	66	9	25	19	6
	mean (μT)	0.07	0.04	0.14	0.18	0.38
Canada	SD	0.06	0.02	0.1	0.2	0.3
London *et al.* (1991)[e]	No. of measurements	19	20	94	108	50
	mean (μT)	0.05	0.05	0.07	0.07	0.12
USA	% > 0.25 μT	0.3	3.7	11.6	6.4	16.6

[a] Childhood cancer. Magnetic fields measured under low power use conditions
[b] 24-h magnetic field measurements in the bedroom
[c] 24-h magnetic field measurements (child's bedroom); % > 0.2 μT not reported
[d] Personal monitoring of controls; SD, standard deviation
[e] 24-h measurements

The concept of wire coding, that is, assessing residential exposure on the basis of the observable characteristics of nearby electrical installations, has been shown to be a usable surrogate when tailored to local wiring practices. However, the so-called Wertheimer and Leeper wire code may not be an adequate surrogate in every environment (see Table 17). In general, wire codes have been used only in North American studies, as their applicability is limited in other countries where power drops to homes are mostly underground.

(iii) *Calculated historical fields*

Feychting and Ahlbom (1993) carried out a case–control study nested in a cohort of residents living in homes within 300 m of power lines in Sweden. The geometry of the conductors on the power line, the distance of the houses from the power lines and historical records of currents, were all available. This special situation allowed the investigators to calculate the fields to which the subjects' homes were exposed at various times (e.g. prior to diagnosis) (Kheifets *et al.*, 1997a).

The common elements between wire coding and the calculation model used by Feychting and Ahlbom (1993) are: the reliance on the basic physical principles that the

field increases with the current and decreases with the distance from the power line, and the fact that both neglect magnetic-field sources other than visible power lines. There is, however, one important difference: in the Wertheimer and Leeper code, the line type and thickness are a measure of the *potential* current carrying capacity of the line. In the Feychting and Ahlbom (1993) study, the approximate yearly average current was obtained from utility records; thus the question of temporal stability of the estimated fields did not even arise: assessment carried out for different times, using different load figures, yielded different estimates.

The approach of Feychting and Ahlbom (1993) has been used in various Nordic countries and elsewhere, although the likely accuracy of the calculations has varied depending in part on the completeness and precision of the available information on historical load. The necessary assumption that other sources of field are negligible is reasonable only for subjects relatively close to high-voltage power lines. The validity of the assumption also depends on details such as the definition of the population chosen for the study and the size of average fields from other sources to which the relevant population is exposed.

There is some evidence from Feychting and Ahlbom (1993) that their approach may work better for single-family homes than for apartments. When Feychting and Ahlbom (1993) validated their method by comparing calculations of present-day fields with present-day measurements, they found that virtually all homes with a measured field < 0.2 μT, whether single-family or apartments, were correctly classified by their calculations. However, for homes with a measured field > 0.2 μT, the calculations were able to classify correctly [85%] of single-family homes, but nearly half of the apartments were misclassified.

The difference between historical calculations and contemporary measurements was also evaluated by Feychting and Ahlbom (1993) who found that calculations using contemporary current loads resulted in a [45%] increase in the fraction of single-family homes estimated to have a field > 0.2 μT, compared with calculations based on historical data. If these calculations of historical fields do accurately reflect exposure, this implies that present-day spot measurements overestimate the number of exposed homes in the past.

(*b*) *Methods involving measurement*

Following the publication of the Wertheimer and Leeper (1979, 1982) studies, doubt was cast on the reported association between cancer and electrical wiring configurations on the grounds that exposure had not been ‘measured’. Consequently, many of the later studies included measurements of various types.

All measurements have the advantage that they capture exposure from whatever sources are present, and do not depend on prior identification of sources, as wire codes and calculated fields do. Furthermore, because measurements can classify fields on a continuous scale rather than in a limited number of categories, they provide greater scope for investigating different thresholds and exposure–response relationships.

(i) *Spot measurements in the home*

The simplest form of measurement is a reading made at a point in time at one place in a home. To capture spatial variations of field, some studies have made multiple spot measurements at different places in or around the home. In an attempt to differentiate between fields arising from sources inside and outside the home, some studies have made spot measurements under 'low-power' (all appliances turned off) and 'high-power' (all appliances turned on) conditions. Neither of these alternatives truly represents the usual exposure conditions in a home, although the low-power conditions are closer to the typical conditions.

The major drawback of spot measurements is their inability to capture temporal variations. As with all measurements, spot measurements can assess only contemporary exposure, and can yield no information about historical exposure, which is an intrinsic requirement for retrospective studies of cancer risk. An additional problem of spot measurements is that they give only an approximation even for the contemporary field, because of short-term temporal variation of fields, and unless repeated throughout the year do not reflect seasonal variations.

A number of authors have compared the time-stability of spot measurements over periods of up to five years (reviewed in Kheifets *et al*., 1997a; UK Childhood Cancer Study Investigators, 2000a). The correlation coefficients reported were from 0.7–0.9, but even correlation coefficients this high may result in significant misclassification (Neutra & DelPizzo, 1996).

(ii) *Longer-term measurements in homes*

Because spot measurements capture short-term temporal variability poorly, many studies have measured fields at one or more locations for longer periods, usually 24–48 h, most commonly in a child's bedroom, which is an improvement on spot measurements. Comparisons of measurements have found only a poor-to-fair agreement between long-term and short-term measurements. This was mainly because short-term increases in fields caused by appliances or indoor wiring do not affect the average field measured over many hours (Schüz *et al*., 2000).

Measurements over 24–48 h cannot account for longer-term temporal variations. One study (UK Childhood Cancer Study Investigators, 1999) attempted to adjust for longer-term variation by making 48-h measurements, and then, for subjects close to high-voltage power lines, modifying the measurements by calculating the fields using historical load data. In a study in Germany, Schüz *et al*. (2001a) identified the source of elevated fields by multiple measurements, and attempted to classify these sources as to the likelihood of their being stable over time. Before beginning the largest study in the USA (Linet *et al*., 1997), a pilot study was conducted (Friedman *et al*., 1996) to establish the proportion of their time children of various ages spent in different parts of the home. These estimates were used to weight the individual room measurements in the main study (Linet *et al*., 1997) for the time-weighted average measure. In

addition, the pilot study documented that magnetic fields in dwellings rather than schools accounted for most of the variability in children's exposure to magnetic fields.

(iii) *Personal exposure monitoring*

Monitoring the personal exposure of a subject by a meter worn on the body is attractive because it captures exposure to fields from all sources. Because all sources are included, the average fields measured tend to be higher than those derived from spot or long-term measurements. However, the use of personal exposure monitoring in case–control studies could be problematic, due to age- or disease-related changes in behaviour. The latter could introduce differential misclassification in exposure estimates. However, personal exposure monitoring can be used to validate other types of measurements or estimates.

(*c*) *Assessment of exposure to ELF electric and magnetic fields from appliances*

The contribution to overall exposure by appliances depends, among other things, on the type of appliance, its age, its distance from the person using it, and the pattern and duration of use. Epidemiological studies have generally relied on questionnaires, sometimes answered by proxies such as other household members (Mills *et al.*, 2000). These questionnaires ascertain some (but not usually all) of these facts, and are subject to recall bias. It is not known how well data from even the best questionnaire approximate to the actual exposure. Mezei *et al*. (2001) reported that questionnaire-based information on appliance use, even when focused on use within the last year, has limited value in estimating personal exposure to magnetic fields. Some limited attempts have been made (e.g. UK Childhood Cancer Study Investigators, 1999) to include some measurements as well as questionnaire data.

Because exposure to magnetic fields from appliances tends to be short-term and intermittent, the appropriate method for combining assessments of exposure from different appliances and chronic exposure from other sources would be particularly dependent on assumptions made about exposure metrics. Such methods have yet to be developed.

2.1.3 *Assessing occupational exposure to magnetic fields*

Following Wertheimer and Leeper's report of an association between residential magnetic fields and childhood leukaemia, Milham (1982, 1985a,b) noted an association between cancer and some occupations (often subsequently called the 'electrical occupations') intuitively expected to involve proximity to sources of electric and magnetic fields. However, classification based on job title is a very coarse surrogate. Critics (Loomis & Savitz, 1990; Guénel *et al.*, 1993a; Thériault *et al.*, 1994) have pointed out that, for example, many electrical engineers are basically office workers and that many electricians work on disconnected wiring.

Intuitive classification of occupations by investigators can be improved upon by taking account of judgements made by appropriate experts (e.g. Loomis *et al.*, 1994a), and by making measurements in occupational groups (e.g. Bowman *et al.*, 1988).

A further improvement is a systematic measurement programme to characterize exposure in a range of jobs corresponding as closely as possible to those of the subjects in a study, thus creating a 'job–exposure matrix', which links measurement data to job titles.

Despite the improvements in exposure assessment, the ability to explain exposure variability in complex occupational environments remains poor. Job titles alone explain only a small proportion of exposure variability. A consideration of the work environment and of the tasks undertaken by workers in a specific occupation leads to a more precise estimate (Kelsh *et al.*, 2000). Harrington *et al.* (2001) have taken this approach one stage further by combining job information with historical information not only on the environment in general but on specific power stations and substations. The within-worker and between-worker variability which account for most of the variation are not captured using these assessments.

It should be noted that even the limited information that is available on occupational exposure is confined almost entirely to the so-called electrical occupations and the power utility workforce. There is evidence (Zaffanella & Kalton, 1998) that workers in some non-electrical occupations are among those most heavily exposed to magnetic fields.

In addition to the need for correct classification of jobs, the quality of occupational exposure assessment depends on the details of work history available to the investigators. The crudest assessments are based on a single job (e.g. as mentioned on a death certificate). This assessment can be improved by identifying the job held for the longest period, or even better, by obtaining a complete job history which would allow for the calculation of the subject's cumulative exposure often expressed in μT–years.

2.1.4 *Assessing exposure to electric fields*

Assessment of exposure to electric fields is generally even more difficult and less well developed than the assessment of exposure to magnetic fields. All of the difficulties encountered in assessment of exposure to magnetic fields discussed above also apply to electric fields. In addition, electric fields are easily perturbed by any conducting object, including the human body. Therefore, the very presence of subjects in an environment means that they are not being exposed to an 'unperturbed field' although most studies that have assessed electric fields have attempted to assess the unperturbed field.

2.2 Cancer in children

2.2.1 *Residential exposure*

(*a*) *Descriptive studies*

In an ecological study in Taiwan, Lin and Lee (1994) observed a higher than expected incidence of childhood leukaemia in five districts in the Taipei Metropolitan Area where a high-voltage power line passed over at least one elementary school campus (standardized incidence ratio [SIR], 1.5; 95% CI, 1.2–1.9; based on 67 cases) for the period 1979–88. In a re-analysis, Li *et al*. (1998) focused on the three districts densely scattered with high-voltage power lines during the period 1987–92 and found an SIR of 2.7 (95% CI, 1.1–5.6) on the basis of seven observed cases versus 2.6 expected cases in all children in Taiwan, living within a distance of 100 m from an overhead power line.

Milham and Ossiander (2001) hypothesized that the emergence of the peak in incidence of acute lymphoblastic leukaemia in children aged 3–4 years may be due to exposure to ELF electric and magnetic fields. The authors examined state mortality rates in the USA during the years 1928–32 and 1949–51 and related this to the percentage of residences within each state with an electricity supply. The peak incidence of acute lymphoblastic leukaemia in children appeared to have developed earlier in those states in which more homes were connected earlier to the electricity supply.

(*b*) *Cohort study*

The only cohort study of childhood cancer and magnetic fields (see Table 18) was conducted by Verkasalo *et al*. (1993) in Finland. The study examined the risk of cancer in children living at any time from 1970–89 within 500 m of overhead high-voltage power lines (110–400 kV), where average magnetic fields were calculated to be ≥ 0.01 μT. The cohort comprised 68 300 boys and 66 500 girls under the age of 20 (contributing 978 100 person–years). During the observation period of 17 years, a total of 140 patients with childhood cancer (35 children with leukaemia, 39 with a tumour of the central nervous system, 15 with a lymphoma and 51 with other malignant tumours) were identified by the Finnish Cancer Registry. Historical magnetic fields were estimated for each year from 1970–89 by the Finnish power company. The dwellings of each child were ascertained from the central population registry and the shortest distance to nearby power lines was calculated by using exact coordinates of homes and power lines. Additional variables used in the calculation of the magnetic field strength were the current flow and the location of phase conductors of each power line. Point estimates of average annual currents for 1984–89 were generated by a power system simulator; information on existing line load was available for 1977–83; and data on power consumption from 1977, corrected for year of construction of power lines, were used to estimate current flow for the years 1970–76. Cumulative exposure was defined as the average exposure per year multiplied by the number of years of exposure (μT–years).

Table 18. Cohort study of childhood cancer and exposure to ELF magnetic fields

Study size, number of cases	Exposure	SIR (95% CI) by cancer site									
		Leukaemia	No. of cases	CNS	No. of cases	Lymphoma	No. of cases	Other sites	No. of cases	All cancers	No. of cases
68 300 boys, 66 500 girls, aged 0–19 years; 140 incident cancer cases diagnosed 1970–89	**Calculated historical magnetic fields**										
	< 0.01 μT (baseline)	1.0		1.0		1.0		1.0		1.0	
	0.01–0.19 μT	0.89 (0.61–1.3)	32	0.85 (0.59–1.2)	34	0.91 (0.51–1.5)	15	1.1 (0.79–1.4)	48	0.94 (0.79–1.1)	129
	≥ 0.2 μT	1.6 (0.32–4.5)	3	2.3 (0.75–5.4)	5	0 (0.0–4.2)	0	1.2 (0.26–3.6)	3	1.5 (0.74–2.7)	11
	Calculated cumulative magnetic fields (μT–years)										
	< 0.01 (baseline)	1.0		1.0		1.0		1.0		1.0	
	0.01–0.39	0.90 (0.62–1.3)	32	0.82 (0.56–1.2)	32	0.88 (0.48–1.5)	14	1.1 (0.80–1.4)	47	0.93 (0.78–1.1)	125
	≥ 0.4	1.2 (0.26–3.6)	3	2.3 (0.94–4.8)	7	0.64 (0.02–3.6)	1	1.0 (0.27–2.6)	4	1.4 (0.77–2.3)	15

From Verkasalo *et al.* (1993), Finland

SIR, standardized incidence ratio; CI, confidence interval; CNS, central nervous system

Expected numbers calculated in sex-specific five-year age groups; no further adjustments. SIRs for highest exposure categories for CNS tumours are questionable, since one boy with three primary tumours was counted three times.

The cut-points chosen to indicate high exposure were ≥ 0.2 μT for average exposure and ≥ 0.4 μT–years for cumulative exposure. The expected number of cases was calculated in five-year age groups by multiplying the stratum-specific number of person–years by the corresponding cancer incidence in Finland. No effect modifiers were considered. Standardized incidence ratios for children exposed to magnetic fields of ≥ 0.2 μT were 1.6 (95% CI, 0.32–4.5) for leukaemia, 2.3 (95% CI, 0.75–5.4) for tumours of the central nervous system (all in boys) and 1.5 (95% CI, 0.74–2.7) for all cancers combined. No child exposed to magnetic fields was diagnosed with lymphoma versus 0.88 expected. The corresponding SIRs with cumulative exposure of ≥ 0.4 μT–years were 1.2 (95% CI, 0.26–3.6) for leukaemia, 2.3 (95% CI, 0.94–4.8) for tumours of the central nervous system, 0.64 (95% CI, 0.02–3.6) for lymphoma and 1.4 (95% CI, 0.77–2.3) for all cancers, respectively. The SIRs in the intermediate category for each metric (0.01–< 0.2 μT, average exposure; 0.01–< 0.4 μT–years, cumulative exposure) were below unity. The SIRs for tumours of the central nervous system require careful interpretation, since one 18-year-old boy with three primary brain tumours and neurofibromatosis type 2 was counted as three cases. If this child were considered as one case, the number of cases of tumours of the central nervous system in exposed children would be reduced from five to three.

(*c*) *Case–control studies*

A number of case–control studies of childhood leukaemia and ELF electric and magnetic fields have been published.

The results of these studies by tumour type (leukaemia and central nervous system) and by magnetic and electric fields are shown in Tables 19–21. The tables show only studies that contributed substantially to the overall summary and only the results of a-priori hypotheses are presented.

The first study of ELF electric and magnetic fields and childhood cancer was conducted in Denver, CO, USA (Wertheimer & Leeper, 1979). The population base consisted of children born in Colorado who resided in the greater Denver area between 1946 and 1973. The cases were all children aged less than 19 years who had died from cancer between 1950 and 1973 (n = 344), including 155 children with leukaemias and 66 with brain tumours, 44 with lymphomas and 63 with cancers of other sites. The controls (n = 344) were selected from two sources: Denver-area birth certificates and listings of all births in Colorado during the time period. Exposure was assessed by using diagrams to characterize electrical wiring configurations near the dwelling occupied by the child at birth and that occupied two years prior to death, or the corresponding dates for matched controls. The wiring was classified as having a high or low current configuration (HCC or LCC). Potential confounding was evaluated by examining the results within strata by age, birth order, social class, urban versus suburban, and heavy traffic areas versus lighter traffic areas. Point estimates were not reported, but p values calculated from chi-square tests were given. The percentage of children living in HCC homes two years before death was 41%, 41% and 46% for

Table 19. Case–control studies of childhood leukaemia and exposure to ELF magnetic fields[a]

Reference, area	Study size (for analyses)	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
Wertheimer & Leeper (1979), Denver, CO, USA	155 deceased cases, 155 controls, aged 0–19 years	**Wire code**			No risk estimates presented; lack of blinding for the exposure assessment; hypothesis-generating study
		LCC	92 (126 controls)		
		HCC	63 (29 controls)		
London *et al*. (1991), Los Angeles County, CA, USA	*Wire code*: 211 cases, 205 controls; *24-h measurements*: 164 cases, 144 controls, aged 0–10 years	**Wire code**			Matched analysis, no further adjustments; low response rates for measurements; no wire coding of subjects who refused to participate
		UG/VLCC (baseline)	31	1.0	
		OLCC	58	0.95 (0.53–1.7)	
		OHCC	80	1.4 (0.81–2.6)	
		VHCC	42	2.2 (1.1–4.3)	
		Mean magnetic fields (24-h bedroom measurement)			
		< 0.067 μT (baseline)	85	1.0	
		0.068–0.118 μT	35	0.68 (0.39–1.2)	
		0.119–0.267 μT	24	0.89 (0.46–1.7)	
		≥ 0.268 μT	20	1.5 (0.66–3.3)	
Feychting & Ahlbom (1993), Sweden (corridors along power lines)	39 cases, 558 controls, aged 0–15 years	**Calculated historical magnetic fields**			Adjusted for sex, age, year of diagnosis, type of house, Stockholm county (yes/no); in subsequent analysis also for socioeconomic status and air pollution from traffic; no contact with subjects required
		< 0.1 μT (baseline)	27	1.0	
		0.1–0.19 μT	4	2.1 (0.6–6.1)	
		≥ 0.2 μT	7	2.7 (1.0–6.3)	

Table 19 (contd)

Reference, area	Study size (for analyses)	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
Olsen *et al*. (1993), Denmark	833 cases, 1666 controls, aged 0–14 years	**Calculated historical magnetic fields**			Adjusted for sex and age at diagnosis; socioeconomic status, distribution similar between cases and controls; no contact with subjects required
		< 0.1 μT (baseline)	829	1.0	
		0.1–0.24 μT	1	0.5 (0.1–4.3)	
		≥ 0.25 μT	3	1.5 (0.3–6.7)	
Tynes & Haldorsen (1997), Norway (census wards crossed by power lines)	148 cases, 579 controls, aged 0–14 years	**Calculated historical magnetic fields**			Adjusted for sex, age and municipality, also for socioeconomic status, type of house, and number of dwellings; no contact with subjects required
		< 0.05 μT (baseline)	139	1.0	
		0.05–< 0.14 μT	8	1.8 (0.7–4.2)	
		≥ 0.14 μT	1	0.3 (0.0–2.1)	
Michaelis *et al*. (1998), Lower Saxony and Berlin (Germany)	176 cases, 414 controls, aged 0–14 years	**Median magnetic fields (bedroom 24-h measurement)**			Adjusted for sex, age and part of Germany (East, West), socioeconomic status and degree of urbanization; information on a variety of potential confounders was available; low response rates
		< 0.2 μT (baseline)	167	1.0	
		≥ 0.2 μT	9	2.3 (0.8–6.7)	

Table 19 (contd)

Reference, area	Study size (for analyses)	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
McBride *et al.* (1999), five Canadian provinces, subjects living within 100 km of major cities, Canada	*Personal monitoring*: 293 cases, 339 controls, aged 0–14 years	**Personal monitoring (48-h)**			Adjusted for age, sex, province, maternal age at birth of child, maternal education, family income, ethnicity and number of residences since birth; information on a variety of potential confounding factors was available; relatively low response rates for the personal monitoring portion; children with Down syndrome excluded from this study
		< 0.08 μT (baseline)	149	1.0	
		0.08–< 0.15 μT	67	0.57 (0.37–0.87)	
		0.15–< 0.27 μT	45	1.1 (0.61–1.8)	
		≥ 0.27 μT	32	0.68 (0.37–1.3)	
	Wire code: 351 cases, 362 controls	**Wire code**			
		UG (baseline)	79	1.0	
		VLCC	73	0.70 (0.41–1.2)	
		OLCC	77	0.76 (0.45–1.3)	
		OHCC	83	0.64 (0.38–1.1)	
		VHCC	39	1.2 (0.58–2.3)	
UKCCSI (1999), England, Wales and Scotland	1073 cases, 1073 controls, aged 0–14 years	**Time-weighted average magnetic fields (1.5–48-h measurement)**			Adjusted for sex, date of birth and region, also for socioeconomic status; information on a variety of potential confounders was available; low reponse rates
		< 0.1 μT (baseline)	995	1.0	
		0.1–< 0.2 μT	57	0.78 (0.55–1.1)	
		≥ 0.2 μT	21	0.90 (0.49–1.6)	
		0.2–< 0.4 μT	16	0.78 (0.40–1.5)	
		≥ 0.4 μT	5	1.7 (0.40–7.1)	

Table 19 (contd)

Reference, area	Study size (for analyses)	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
Schüz *et al*. (2001a), West Germany	514 cases, 1301 controls, aged 0–14 years	**Median magnetic fields (24-h bedroom measurement)**			Adjusted for sex, age, year of birth, socioeconomic status and degree of urbanization; information on a variety of potential confounders was available; low response rates; relatively long time lag between date of diagnosis and date of the measurement
		< 0.1 μT (baseline)	472	1.0	
		0.1–< 0.2 μT	33	1.2 (0.73–1.8)	
		0.2–< 0.4 μT	6	1.2 (0.43–3.1)	
		≥ 0.4 μT	3	5.8 (0.78–43)	
		Night-time magnetic fields			
		< 0.1 μT (baseline)	468	1.0	
		0.1–< 0.2 μT	34	1.4 (0.90–2.2)	
		0.2–< 0.4 μT	7	2.5 (0.86–7.5)	
		≥ 0.4 μT	5	5.5 (1.2–27)	

Table 19 (contd)

Reference, area	Study size (for analyses)	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
Linet *et al.* (1997), nine mid-western and mid-Atlantic states, USA	*Wire code*: 408 cases, 408 controls, aged 0–14 years; *24-h measurements*: 638 cases, 620 controls	**Time-weighted average (24-h bedroom measurement plus spot measurements in two rooms)**		Unmatched		Matched	Unmatched analysis additionally adjusted for age, sex, mother's education and family income; information on a variety of potential confounding factors was available; wire coding of subjects who refused to participate; relatively low response rates for the measurements in controls; only acute lymphoblastic leukaemia; children with Down syndrome excluded from this study (Schüz *et al.*, 2001a)
		< 0.065 μT (baseline)	267	1.0	206	1.0	
		0.065–0.099 μT	123	1.1 (0.81–1.5)	92	0.96 (0.65–1.4)	
		0.100–0.199 μT	151	1.1 (0.83–1.5)	107	1.2 (0.79–1.7)	
		≥ 0.200 μT	83	1.2 (0.86–1.8)	58	1.5 (0.91–2.6)	
		Wire code					
		UG/VLCC (baseline)			175	1.0	
		OLCC			116	1.1 (0.74–1.5)	
		OHCC			87	0.99 (0.67–1.5)	
		VHCC			24	0.88 (0.48–1.6)	

UG, underground wires; VLCC, very low current configuration; OLCC, ordinary low current configuration; OHCC, ordinary high current configuration; VHCC, very high current configuration; LCC, low current configuration; HCC, high current configuration; UKCCSI, UK Childhood Cancer Study Investigators

[a] In these tables, only studies that contributed substantially to the overall summary were considered; only results that were part of the analysis strategy defined above are presented; exposure metrics and cut-points vary across studies, for a better comparison, please refer to Table 23.

Table 20. Case–control studies of childhood tumours of the central nervous system and exposure to ELF magnetic fields

Reference, area	Study size	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
Wertheimer & Leeper (1979), Denver, CO, USA	66 deceased cases, 66 controls, aged 0–19 years	**Wire code**			No risk estimates presented; lack of blinding for the exposure assessment; hypothesis-generating study
		LCC	36 (49 controls)		
		HCC	30 (17 controls)		
Feychting & Ahlbom (1993), Sweden (corridors along power lines)	33 cases, 558 controls, aged 0–15 years	**Calculated historical magnetic fields**			Adjusted for sex, age, year of diagnosis, type of house, Stockholm county (yes/no); in subsequent analysis also for socioeconomic status and air pollution from traffic; no contact with subjects required
		< 0.1 μT (baseline)	29	1.0	
		0.1–0.19 μT	2	1.0 (0.2–3.8)	
		≥ 0.2 μT	2	0.7 (0.1–2.7)	
Olsen *et al*. (1993), Denmark	624 cases, 1872 controls, aged 0–14 years	**Calculated historical magnetic fields**			Adjusted for sex and age at diagnosis; socioeconomic distribution similar among cases and controls; no contact with subjects required
		< 0.1 μT (baseline)	621	1.0	
		0.1–0.24 μT	1	1.0 (0.1–9.6)	
		≥ 0.25 μT	2	1.0 (0.2–5.0)	
Preston-Martin *et al*. (1996a), Los Angeles County, CA, USA	298 cases, 298 controls, aged 0–19 years	**Mean magnetic fields (24-h bedroom)**			Adjusted for age, sex, birth year, socioeconomic status, maternal waterbed use; low response rates for measurements
		0.010–0.058 μT (baseline)	48	1.0	
		0.059–0.106 μT	29	1.5 (0.7–3.0)	
		0.107–0.248 μT	16	1.2 (0.5–2.8)	
		0.249–0.960 μT	13	1.6 (0.6–4.5)	
		Wire code			
		UG	39	2.3 (1.2–4.3)	
		VLCC/OLCC (baseline)	114	1.0	
		OHCC	97	0.8 (0.6–1.2)	
		VHCC	31	1.2 (0.6–2.2)	

Table 20 (contd)

Reference, area	Study size	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
Gurney *et al*. (1996), Seattle, WA, USA	133 cases, 270 controls, aged 0–19 years	**Wire code**			Unadjusted, but evaluated for confounding by age, sex, race, county, reference year, mother's education, family history of brain tumours, passive smoking, farm residence, history of head injury, X-rays, epilepsy
		UG (baseline)	47	1.0	
		VLCC	39	1.3 (0.7–2.1)	
		OLCC	11	0.7 (0.3–1.6)	
		OHCC	19	1.1 (0.6–2.1)	
		VHCC	4	0.5 (0.2–1.6)	
Tynes & Haldorsen (1997), Norway (census wards crossed by power lines)	156 cases, 639 controls, aged 0–14 years	**Historical calculated magnetic fields**			Adjusted for sex, age and municipality, also for socioeconomic status, type of house, and number of dwellings; no contact with subjects required
		< 0.05 μT (baseline)	144	1.0	
		0.05–< 0.14 μT	8	1.9 (0.8–4.6)	
		≥ 0.14 μT	4	0.7 (0.2–2.1)	
UKCCSI (1999), England, Wales and Scotland	387 cases, 387 controls, aged 0–14 years	**Time-weighted average magnetic fields (1.5–48-h measurement)**			Adjusted for sex, date of birth, and region, also for socioeconomic status; information on a variety of potential confounders was available; low reponse rates; no exposure to magnetic fields ≥ 0.4 μT
		< 0.1 μT (baseline)	359	1.0	
		0.1–< 0.2 μT	25	2.4 (1.2–5.1)	
		≥ 0.2 μT	3	0.46 (0.11–1.9)	
		0.2–< 0.4 μT	3	0.70 (0.16–3.2)	
Schüz *et al*. (2001b), Lower Saxony and Berlin (Germany)	64 cases, 414 controls, aged 0–14 years	**Median magnetic fields (24-h bedroom measurement)**			Adjusted for sex, age, part of Germany (East, West), socioeconomic status and degree of urbanization; information on a variety of potential confounders was available; low response rates; same control group as for leukaemia cases (Michaelis *et al*., 1998)
		< 0.2 μT (baseline)	62	1.0	
		≥ 0.2 μT	2	1.7 (0.32–8.8)	

UG, underground wires; VLCC, very low current configuration; OLCC, ordinary low current configuration; OHCC, ordinary high current configuration; VHCC, very high current configuration; UKCCSI, UK Childhood Cancer Study Investigators

Table 21. Case–control studies of childhood leukaemia and exposure to ELF electric fields

Reference, area	Study size (for analyses)	Exposure	No. of cases	Risk estimates: odds ratio (95% CI)	Comments
London *et al*. (1991), Los Angeles County, CA, USA	**Spot measurements (child's bedroom)** 136 cases, 108 controls, aged 0–10 years	< 50th percentile (baseline) 50–74th percentile (baseline) 75–89th percentile (baseline) ≥ 90th percentile (baseline)	NR	1.0 0.66 (0.36–1.2) 1.1 (0.58–2.6) 0.44 (0.19–1.0)	Matched analysis, no further adjustments; low response rates for measurements; no wire coding of subjects who refused to participate
McBride *et al.* (1999), five Canadian provinces, subjects living within 100 km of major cities, Canada	**Personal monitoring** 274 cases, 331 controls, aged 0–14 years	< 12.2 V/m (baseline) 12.2–< 17.2 V/m 17.2–< 24.6 V/m 24.6–64.7 V/m	143 64 39 28	1.0 0.79 (0.51–1.2) 0.76 (0.45–1.2) 0.82 (0.45–1.5)	Adjusted for age, sex, province, maternal age at birth of child, maternal education, family income, ethnicity and number of dwellings since birth; children with Down syndrome excluded from this study

NR, not reported

children with leukaemia, lymphoma and brain tumours, respectively, compared with 19%, 25% and 26% in the controls. Forty-four per cent of 109 cases and 20.3% of 128 controls with stable dwellings had HCC wiring configurations ($p < 0.001$). The results were similar when birth addresses were used. When exposure was further subdivided into the categories of substation (highest exposure), other HCC, LCC except end poles and end poles, the percentage of children with cancer declined with lower wiring configuration. The results also appeared to be fairly consistent within broad categories of potential confounding variables. [The Working Group noted that the wire-coding technicians in this study were not blinded as to the status of cases or controls leading to potential bias in exposure assessment.]

Fulton *et al*. (1980) conducted a case–control study in Rhode Island, USA. Patients with leukaemia aged between 0 and 20 years were identified from the records of the Rhode Island Hospital from 1964–78. Out of 155 cases, a total of 119 were selected and 36 cases who had resided out of the state for part of the eight years preceding diagnosis were excluded. The analysis was based on dwellings, not individuals, and 209 case dwellings were included. Two hundred and forty control addresses were selected from Rhode Island birth certificates. Two controls were matched to each case on year of birth. The authors obtained complete address histories for cases, but not for controls. Exposure assessment consisted of mapping the power lines situated within 50 yards (45.72 m) of each residence and categorizing the expected current according to a method of wire coding. A total of 95% of case and 94% of control addresses were successfully mapped. The association between exposure category and childhood leukaemia was tested by means of chi-square tests. The analysis showed no relationship between childhood leukaemia and exposure category. [The Working Group noted that the shortcomings of this study include lack of comparability of cases and controls, analysis by dwelling as opposed to by individual and the lack of control for confounding.]

The first European study on childhood leukaemia and exposure to magnetic fields was carried out in Sweden (Tomenius, 1986). The study included children aged between 0 and 18 years with benign and malignant tumours. The children had been born and diagnosed in the county of Stockholm and were registered with the Swedish Cancer Registry during the years 1958–73. A total of 716 children of whom 660 had a malignant tumour were included. For each case, a control matched for sex, age and church district of birth was selected from birth registration records held in the same parish office. The controls had been born just before or after the child with a tumour and still lived in Stockholm county at the date of diagnosis of the corresponding case. The analysis was based on dwellings rather than individuals. A total of 1172 dwellings were included for cases and 1015 dwellings for controls. Almost all (96%) dwellings were visited to determine their proximity to different types of electrical installation (200-kV power lines, 6–< 200-kV power lines, substations, transformers, electric railways, underground railways). Spot measurements of peak magnetic field were conducted outside the entrance door. From magnetic field measurements, the odds

ratios in those children exposed to magnetic fields of ≥ 0.3 μT were 0.3 for leukaemia, 1.8 for lymphoma, 3.7 for cancer of the central nervous system ($p < 0.05$) and 2.1 for all tumours combined ($p < 0.05$). An excess tumour risk was also reported for children living less than 150 m from a 200-kV power line, but this was because the observed number of case dwellings located 100–150 m from a power line was higher than expected, while the number of case dwellings located within 100 m from a power line was as expected. [The Working Group noted that outdoor spot measurements, sometimes made more than 30 years after the etiologically relevant time period, are a poor proxy for an individual's exposure to magnetic fields. Another limitation is that the analyses are based on dwellings rather than individuals, and that the numbers of dwellings were different for cases and controls.]

Savitz *et al*. (1988) carried out a second study in the Denver, CO, area during the 1980s. The population base consisted of all children < 15 years of age residing in the 1970 Denver Standard Metropolitan Statistical Area. A total of 356 cases of childhood cancers diagnosed from 1976–1983 were identified from the Colorado Central Cancer Registry and from records of area hospitals. A total of 278 potential controls were identified through random digit dialling and were matched to the cases by age (± 3 years), sex and telephone exchange. The cases had been diagnosed up to nine years prior to selection, so controls had to be restricted to those who still lived in the same residence as they had done at the time the case was diagnosed. Exposure to electric fields was assessed by means of spot measurements under 'high-power' conditions (when selected appliances and lights were turned on) and exposure to magnetic fields by means of spot measurements under both 'high-power' and 'low-power' conditions (when most appliances and lights were turned off). The measurements were made in the current dwelling of the case if it was also the dwelling occupied prior to diagnosis, and homes were classified by Wertheimer-Leeper wire codes. A total of 252 (70.8%) of the cases were interviewed; spot measurements of fields were made for 128 cases (36%) and wire coding was completed for 319 (89.6%). Two hundred and twenty-two controls were interviewed, giving a final response rate from the random-digit dialling phase of 63%; a total of 207 (74.5%) of the controls had spot measurements made in their homes and the homes of 259 (93.2%) were wire coded. Potential confounding variables included year of diagnosis and residential stability; electric load at the time of measurement; parental age, race, education and income; traffic density, and various in-utero exposures. For low-power conditions, the odds ratios for magnetic field measurements of ≥ 0.2 μT versus < 0.2 μT were 1.4 (95% CI, 0.63–2.9) for all cancers combined, 1.9 (95% CI, 0.67–5.6) for leukaemia, 2.2 (95% CI, 0.46–10) for lymphoma and 1.0 (95% CI, 0.22–4.8) for brain cancer. The odds ratios for high-power conditions were near unity for most cancer sites, and those for high electric fields were mostly below unity. For assessment of the influence of wire codes, underground wires were considered to have the lowest magnetic fields. The odds ratios for 'high' (HCC and VHCC) versus 'low' (underground, VLCC and LCC) wire codes were 1.5 (95% CI, 1.0–2.3) for all cancers combined, 1.5 (95% CI,

0.90–2.6) for leukaemia, 0.8 (95% CI, 0.29–2.2) for lymphoma and 2.0 (95% CI, 1.1–3.8) for brain cancer. For VHCC versus buried wires, the odds ratios were 2.2 (95% CI, 0.98–5.2) for all cancers, 2.8 (95% CI, 0.94–8.0) for leukaemia, 3.3 (95% CI, 0.80–14) for lymphoma and 1.9 (95% CI, 0.47–8.0) for brain cancer. [The Working Group noted the differential residential requirements for controls compared with cases, leading to a possible selection bias. Spot measurements were taken only in dwellings that were still occupied by the cases, although many years might have elapsed since the date of diagnosis (measurements were made for only 36% of the eligible cases) and in many instances, measurements were made years after the etiological time period of interest.]

Coleman *et al*. (1989) conducted a registry (Thames Cancer Registry)-based case–control study in the United Kingdom. The study included leukaemia patients of all ages diagnosed between 1965 and 1980 and resident in one of four adjacent London boroughs. Two tumour controls were selected randomly from the same registry and matched to each case for sex, age and year of diagnosis. The childhood study population comprised 84 leukaemia cases and 141 cancer controls under the age of 18. Only one case and one control lived within 100 m of an overhead power line; thus, no risk estimates were presented for proximity to power lines. No clear pattern was seen for children living within 100 m of a substation.

The second case–control study in the United Kingdom was carried out by Myers *et al*. (1990) on children born within the boundaries of the Yorkshire Health Region and registered in the period 1970–79. A total of 419 cases and 656 controls were identified, but some could not be located, and 374 cases (89%) and 588 (90%) controls were finally analysed. Exposure was assessed by calculations of historical magnetic fields due to the load currents of overhead power lines at the birth addresses of the children, on the basis of line-network maps and load records. Risk estimates were presented for all cancers, and separately for non-solid tumours (mostly leukaemia and lymphoma) and solid tumours (all brain tumours, neuroblastomas and tumours of other sites). For all cancers combined, for children in the group calculated to have the highest exposure to magnetic fields, i.e. ≥ 0.1 μT, the resulting odds ratio was 0.4 (95% CI, 0.04–4.3). For the two diagnostic subgroups, non-solid tumours and solid tumours, a cut-point of ≥ 0.03 μT was chosen and the respective odds ratios were 1.4 (95% CI, 0.41–5.0) and 3.1 (95% CI, 0.31–32). The distance analysis with a cut-point of < 25 m gave an odds ratio of 1.1 (95% CI, 0.47–2.6) for all cancers combined.

The first North American study to include long-term measurements of ELF magnetic fields was carried out by London *et al*. (1991, 1993) in Los Angeles, CA. The study population consisted of children from birth to the age of 10 years who had resided in Los Angeles County. A total of 331 cases of childhood leukaemia were identified by the Los Angeles County Cancer Surveillance Program from 1980–87. A total of 257 controls were identified, using a combination of friends of the patients and random digit dialling. The cases and controls were individually matched on age, sex and ethnicity. Exposure assessment consisted of spot measurements of electric and

magnetic fields in three or four locations inside the home and three locations outside, a 24-h magnetic field measurement made in the child's bedroom and wire coding. Lifetime residential histories were obtained, and measurements were sought for at least one dwelling per subject. Spot measurements were made in multiple residences when possible. Latency was considered in the design phase by defining an 'etiological time-period' that extended from birth up to a reference date that depended upon the child's age at diagnosis. The same reference date was used for each matched control. The response rates for cases for the various parts of the study were approximately 51% for the 24-h measurement and about 66% for wire coding. [The Working Group noted that it was not possible to calculate accurate response rates for the controls.] Twenty-four-hour measurements for both cases and controls were analysed according to percentile cut-points (< 50th (< 0.07 μT), 50–74th, 75–89th and ≥ 90th (≥ 0.27 μT)). When compared with the referent group of < 50th percentile, the odds ratios for each category were 0.68 (95% CI, 0.39–1.2), 0.89 (95% CI, 0.46–1.7) and 1.5 (95% CI, 0.66–3.3) in relation to the arithmetic mean of 24-h measurements of magnetic field in the child's bedroom. When compared with a referent group with VLCC and underground wire codes, the odds ratios for OLCC, OHCC and VHCC were 0.95 (95% CI, 0.53–1.7), 1.4 (95% CI, 0.81–2.6) and 2.2 (95% CI, 1.1–4.3). Adjustment for confounding variables reduced the estimate for VHCC from 2.2 to 1.7 (95% CI, 0.82–3.7), but the trend was still statistically significant. There was no significant association of childhood leukaemia with spot measurements of magnetic or electric fields. [The Working Group considered that the limitations of this study include somewhat low response rates for the measurement component of the study.]

Ebi *et al.* (1999) re-analysed the Savitz *et al.* (1988) and London *et al.* (1991) studies using the 'case-specular method'. This method compared the wire codes of subjects' homes with those of 'specular residences': imaginary homes constructed as a mirror image of the true home, symmetrical with respect to the centre of the street. This method is intended to discriminate between the 'neighbourhood variables', which are normally the same for the true home and its mirror image, and the effects of power lines that are normally not placed symmetrically in the centre of the street. The study confirmed the association reported in the original studies. [The Working Group noted that this study did not correct for limitations noted for the original studies and did not address selection bias.]

Feychting and Ahlbom (1993) conducted a population-based nested case–control study in Sweden. The study base consisted of all children aged less than 16 years who had lived on a property at least partially located within 300 m of any 220- or 400-kV power lines from 1960–85. They were followed from the time they moved into the corridor until the end of the study period. The Swedish population registry was used to identify individuals who had lived on the respective properties, and record linkage to the Swedish Cancer Registry was performed to identify patients with childhood cancer among this group. A total of 142 children with cancer were identified within the power-line corridors, 39 of whom were diagnosed as having leukaemia, 33 as

having a tumour of the central nervous system, 19 as having a lymphoma and 51 as having some other type of cancer. Approximately four controls per case, matched according to age, sex, parish of residence during the year of diagnosis or during the last year before the case moved to a new home, and proximity to the same power line, were selected randomly from the study base, providing a total of 558 controls. Exposure to magnetic fields was assessed by calculated historical fields, calculated contemporary fields and spot measurements under low-power conditions within the dwelling. To calculate historical fields, information on the average power load on each power line was obtained for each year. Spot measurements were made with a meter, constructed specifically for the purpose of this study, in the home within the power-line corridor where the child lived at the time closest to diagnosis. Spot measurements were conducted 5–31 years after diagnosis [the participation rate was 63% among cases and 62% among controls]. In the analysis, the authors placed most emphasis on calculated historical fields using a three-level exposure scale with categories of < 0.1 μT, 0.1–< 0.2 μT and ≥ 0.2 μT. The relative risks were calculated by using a logistic regression model stratified according to age, sex, year of diagnosis, type of house (single-family house or apartment), and whether or not the subject lived within the county of Stockholm. Other potential effect modifiers considered in the analysis were socioeconomic status taken from the population censuses made closest to the year of birth and closest to the year of diagnosis of cancer, and air pollution from traffic estimated by the Swedish Environmental Protection Board. Cancer risk in relation to calculated magnetic fields closest in time to diagnosis at ≥ 0.2 μT compared with < 0.1 μT was elevated for childhood leukaemia (odds ratio, 2.7; 95% CI, 1.0–6.3; 7 cases) but not for tumours of the central nervous system (odds ratio, 0.7; 95% CI, 0.1–2.7; 2 cases), lymphoma (odds ratio, 1.3; 95% CI, 0.2–5.1; 2 cases) or all cancers combined (odds ratio, 1.1; 95% CI, 0.5–2.1; 12 cases). At ≥ 0.3 μT compared with < 0.1 μT, the increased risk for leukaemia was more pronounced with an odds ratio of 3.8 (95% CI, 1.4–9.3; 7 cases), while the risks for the other types of cancer were only slightly altered. Subgroup analysis revealed the highest odds ratios for children aged 5–9 years at date of diagnosis and for children living in single-family homes. Spot measurements showed a good agreement with calculated contemporary fields, demonstrating that calculated fields could predict residential magnetic fields, but agreement with calculated historical fields was poor. Based on a distance of ≤ 50 m compared with > 100 m to nearby power lines, the odds ratio was 2.9 (95% CI, 1.0–7.3; 6 exposed cases, 34 controls) for leukaemia, 1.0 (95% CI, 0.5–2.2; 9 cases, 34 controls) for all cancers and 0.5 (95% CI, 0.0–2.8; 1 case, 34 controls) for tumours of the central nervous system.

The results of a similar population-based case–control study were published in the same year by Olsen *et al*. (1993). The study population included all Danish children under the age of 15 years who had been diagnosed as having leukaemia, a tumour of the central nervous system or malignant lymphoma during the period 1968–86. A total of 1707 patients was identified from the Danish Cancer Registry, of whom 833 had a

leukaemia, 624 had a tumour of the central nervous system and 250 had a malignant lymphoma. Two controls for each patient with leukaemia, three controls for each patient with a tumour of the central nervous system and five controls for each patient with a lymphoma were drawn at random from the files of the Danish central population registry. The matching criteria chosen were sex and date of birth within one year. The total number of controls was 4788. The residential histories of each family were ascertained restrospectively from the date of diagnosis to nine months before the child's birth. Each address was checked against maps of existing or former 50–400-kV power lines, and areas of potential exposure to magnetic fields ≥ 0.1 μT were defined. For all dwellings outside the potential exposure areas, the magnetic fields were assumed to be zero. For other dwellings, historical fields were calculated taking into account the annual average current flow of the line, the type of pylon, the category of the line, the ordering of the phases and any reconstructions. The basic measure of exposure was the average magnetic field generated from a power line to which the child was ever exposed. Exposure was categorized into the groups < 0.1 μT, 0.1–< 0.25 μT and ≥ 0.25 μT. The cumulative dose of magnetic fields was obtained by multiplying the number of months of exposure by the average magnetic field at the dwelling (μT–months). Odds ratios were derived from logistic regression models adjusted for sex and age at diagnosis. The distribution of cases and controls according to socio-economic group did not differ. Odds ratios at calculated field levels of ≥ 0.25 μT compared with < 0.1 μT were 1.5 (95% CI, 0.3–6.7) for leukaemia based on three exposed cases and four exposed controls, 1.0 (95% CI, 0.2–5.0) for tumours of the central nervous system (2 cases, 6 controls) and 5.0 (0.3–82) for malignant lymphoma (1 case, 1 control). In a post-hoc analysis comparing calculated field levels of ≥ 0.4 μT with the same baseline, the respective odds ratios were 6.0 (95% CI, 0.8–44; 3 cases) for leukaemia, 6.0 (95% CI, 0.7–44; 2 cases) for tumours of the central nervous system, 5.0 (95% CI, 0.3–82; 1 case) for malignant lymphoma and 5.6 (95% CI, 1.6–19) for the combined groups based on only six exposed cases and three exposed controls. The distribution functions of cumulative doses of magnetic fields for cases and controls showed that doses were generally higher among cases; but there was never any significant association with an increase in risk.

Coghill *et al*. (1996) conducted a small case–control study in the United Kingdom involving 56 patients with leukaemia and 56 controls. Patients with leukaemia diagnosed between 1985 and 1995 were recruited by media advertising, personal introduction and with the support of the Wessex Health Authority and various self-help groups. Controls of the same age and sex were suggested by the parents of the patients (friend controls). Measurements of the magnetic field (mean, 0.070 μT for the cases, 0.057 μT for the controls) were conducted in the child's bedroom between 20:00 and 08:00. The main result of a conditional logistic regression analysis was an association between leukaemia and electric fields of ≥ 20 V/m with an odds ratio of 4.7 (95% CI, 1.2–28) and somewhat weaker associations in groups with intermediate exposures of 10–19 V/m (odds ratio, 2.4; 95% CI, 0.79–8.1) and of 5–9 V/m (odds

ratio, 1.5; 95% CI, 0.47–5.1), suggesting a dose–response relationship. No association was seen between leukaemia and magnetic fields. [The Working Group noted the potential lack of comparability of cases and controls.]

A study of 298 children with brain tumours (ICD-9 191, 192) and 298 control children was carried out in Los Angeles, CA, by Preston-Martin *et al*. (1996a). The study subjects were aged 19 years or younger, resident in Los Angeles County and diagnosed between 1984 and 1991. Controls were identified by random digit dialling and matched on age and sex. The response rates were about 70% for both cases (298/437) and controls (298/433). Cases and controls were accrued prospectively from 1989 onwards, but retrospectively from 1984 to 1988. The authors attempted to obtain exterior spot measurements and wire codes for all the homes occupied by subjects from conception until diagnosis of brain tumour. The 596 (298 cases, 298 controls) study subjects reported living in a total of 2000 homes; of these, some measurements were made or wire codes were assigned for 1131. No measurements or wire coding were attempted if the former home was outside Los Angeles County. Interior 24-h measurements were made in the child's bedroom and one other room if at the time of interview the child still occupied a home lived in prior to diagnosis. Interior measurements were available for 110 cases (37% of those interviewed) and 101 controls (34% of those interviewed). Wire codes were available for at least one residence for 292 cases (98%) and 269 controls (90%) and exterior spot measurements, made at the front door, were available for 255 cases (86%) and 208 controls (70%). There was no association between living in a home with a wire code of VHCC at diagnosis and childhood brain tumours (odds ratio for VHCC versus VLCC and OLCC, 1.2; 95% CI , 0.6–2.2; 31 cases), adjusted for age, sex, year of birth, socioeconomic status and maternal use of a water bed during pregnancy. The data showed an increased risk for subjects living in homes with underground wiring (odds ratio, 2.3; 95% CI, 1.2–4.3; 39 cases); but this increased risk was apparent only in cases diagnosed before 1989 (odds ratio, 4.3; 95% CI, 1.6–11; 28 cases). There was no increased risk associated with the measurements of magnetic field taken outside the home occupied at the time of diagnosis. The odds ratio was 0.7 (95% CI, 0.3–1.5) for front door measurements > 0.2 μT (13 cases) and 0.9 (95% CI, 0.3–3.2) for fields over 0.3 μT (7 cases). For 24-h means over 0.2 μT in the child's bedroom, the odds ratio was 1.2 (95% CI, 0.5–2.8; 16 cases) and, for fields over 0.3 μT, the odds ratio was 1.7 (95% CI, 0.6–5.0; 12 cases). [The Working Group considered that the limitations of this study included relatively low response rates for both cases and controls, in particular for the interior measurement portion of the study. There is also some indication of bias in the control selection process, as manifested by the different results for underground wiring between cases diagnosed before and after 1989.]

Gurney *et al*. (1996) studied childhood brain tumours in relation to ELF magnetic fields in the Seattle, WA, area of the USA. Patients under 20 years of age were identified through a population-based registry. One hundred and thirty-three of a total of 179 identified cases (74%), and 270 of 343 controls (79%), identified through

random digit dialling, participated in the study. Magnetic field exposure was assessed by wire coding of homes occupied by cases and controls at the diagnosis or reference date. There was no evidence of an association between risk for brain tumour and wire codes. The odds ratio for VHCC homes was 0.5 (95% CI, 0.2–1.6; 4 cases) and, when wire codes were classified into high and low exposure categories, the odds ratio was 0.9 (95% CI, 0.5–1.5; 23 cases). When wire codes for the homes of eligible non-participants were included in the calculations, the odds ratios were similar. [The Working Group noted that cases had lived in their homes for an average of 12 months longer than controls, suggesting the possibility of selection bias.]

In a hospital-based case–control study on childhood leukaemia in Greece, the possible relationship between childhood leukaemia and residential proximity to power lines was investigated (Petridou *et al*., 1997). The study population comprised 117 out of 153 (76%) incident leukaemia cases in children under the age of 15 years diagnosed in 1993–94 and identified by a nationwide network of paediatric oncologists, and two controls per case (202/306; 66%). For every study participant, the Public Power Cooperation of Greece specified the distance between the centre of the dwelling and the two closest power lines between 0.4 and 400 kV (blindly as to status as case or control). From this information, the voltage of each of the two closest power lines was divided by the distance (V/m) and the maximum of the two values was taken as the subject's exposure (modified distance measure). The same procedure was performed by dividing the voltage level of each power line by the square of the distance (V/m^2) and the cube of the distance (V/m^3). Compared with the first quintile, odds ratios for V/m^2 were 0.58 (95% CI, 0.24–1.4), 0.65 (95% CI, 0.26–1.6), 1.5 (95% CI, 0.58–3.8) and 1.7 (95% CI, 0.67–4.1) for the 2nd, 3rd, 4th and 5th quintile, respectively (*p* value for trend = 0.08). The Wertheimer-Leeper wire code was adapted to conditions in Greece. The odds ratios for the four levels in ascending order of magnetic field strength were 0.99 (95% CI, 0.54–1.8), 1.8 (95% CI, 0.26–13), 4.3 (95% CI, 0.94–19) and 1.6 (95% CI, 0.26–9.4); *p* value for trend = 0.17). [The Working Group noted that the main limitation of the study was the crude exposure assessment.]

Tynes and Haldorsen (1997) reported the results from a nested case–control study in Norway. The cohort comprised children under the age of 15 years who had lived in a census ward crossed by a power line (45 kV or greater in urban areas, 100 kV or greater in rural areas) during at least one of the years 1960, 1970, 1980, 1985, 1987 or 1989. Cancer cases occurring in the study area between 1965 and 1989 were identified by record linkage with the Cancer Registry of Norway. Out of 532 children with cancer, 500 were included in the study, of whom 148 had a leukaemia, 156 had a brain tumour, 30 had a lymphoma and 166 had cancer at another site. For each case, one to five controls (depending on eligibility) matched for sex, year of birth and municipality were selected at random from the cohort, resulting in a total of 2004 controls. Exposure was assessed by calculating historical magnetic fields based on the historical current load on the line, the height of the towers and ordering and distance between phases for every power line of 11 kV or greater. The exposure metric was

validated by comparing calculated contemporary fields with magnetic fields measured for 65 schoolchildren who wore personal dosimeters for 24 h. The validation study showed a good agreement between the measured and the calculated magnetic fields. Time-weighted average (TWA) exposure to calculated magnetic fields as well as calculated magnetic fields closest in time to diagnosis were categorized into the groups < 0.05 μT, 0.05–< 0.14 μT and ≥ 0.14 μT. The odds ratio was computed by conditional logistic regression models for matched sets. Effect modifiers considered in additional analyses included socioeconomic status based on the occupation of the father (from the National Central Bureau of Statistics), type of building and number of dwellings. The risk for all cancers combined at TWA exposure ≥ 0.14 μT was estimated to be 0.9 (95% CI, 0.5–1.8) based on 12 exposed cases and 51 exposed controls. The odds ratios for the different types of cancer were 0.3 (95% CI, 0.0–2.1; 1 case) for leukaemia, 0.7 (95% CI, 0.2–2.1; 4 cases) for brain tumour, 2.5 (95% CI, 0.4–16; 2 cases) for lymphoma and 1.9 (95% CI, 0.6–6.0; 5 cases) for cancers at other sites. At a TWA exposure of ≥ 0.2 μT, the odds ratio for children with leukaemia was 0.5 (95% CI, 0.1–2.2; 2 cases). On the basis of the magnetic field exposure closest in time to diagnosis, the odds ratios at ≥ 0.14 μT were generally close to unity (brain tumour, 1.1 (95% CI, 0.5–2.5; 9 cases), lymphoma, 1.2 (95% CI, 0.2–6.4; 2 cases), leukaemia, 0.8 (95% CI, 0.3–2.4; 4 cases), all cancers combined, 1.3 (95% CI, 0.8–2.2; 24 cases), with the exception of cancers at other sites where the odds ratio was 2.5 (95% CI, 1.1–5.9; 9 cases). The cancer risk in relation to calculated magnetic fields of ≥ 0.14 μT during the first year of a child's life was 0.8 (95% CI, 0.1–7.1; 1 case) for leukaemia, 2.3 (0.8–6.6; 7 cases) for tumours of the central nervous system and 2.0 (0.9–4.2; 12 cases) for all cancers combined. A distance from nearby power lines of ≤ 50 m was associated with a significantly enhanced odds ratio of 2.8 (95% CI, 1.5–5.0; 23 cases) for tumours at other sites, but the odds ratio was not significantly different for leukaemia (0.6; 95% CI, 0.3–1.3; 9 cases), brain tumour (0.8; 95% CI, 0.4–1.6; 14 cases) or lymphoma (1.9; 95% CI, 0.6–6.4; 5 cases). The exposure to electric fields was also calculated, but since shielding between houses and power lines was not accounted for, the figures were not used in the risk analysis.

Linet *et al*. (1997) conducted a large study of acute lymphoblastic leukaemia in children in nine mid-western and mid-Atlantic states in the USA between 1989 and 1994 (the NCI (National Cancer Institute)/CCG (Children's Cancer Group) study). The eligible patients were less than 15 years of age and resided in one of the nine states at the time of diagnosis. Controls were selected by random-digit dialling and matched to the cases on age, ethnicity and telephone exchange. Exposure assessment consisted of spot measurements of magnetic fields in three rooms under normal and low-power conditions and outside the front door, and a 24-h measurement made under the child's bed. Wire codes were also noted. For children under the age of five years, measurements were taken in homes that they had occupied for at least six months, if the residences available for measurements collectively accounted for at least 70% of the child's lifetime from conception to the date of diagnosis. For children over the age of

five years, measurements were made for a maximum of two homes occupied during the five years prior to diagnosis, and these homes had to account for at least 70% of the five-year 'etiological time period'. For the wire-coding portion of the study, one dwelling was selected that accounted for at least 70% of the child's lifetime (children < 5 years) or at least 70% of the five years prior to diagnosis for children ≥ 5 years. Thus, this study focused on residentially stable children, particularly for the wire-code part of the study. Measurements were made in the homes of 638 cases and 620 controls (78% and 63% response rates, respectively, according to the eligibility criteria described by Kleinerman *et al.*, 1997). The homes of 408 matched pairs were wire coded. Subjects who refused to participate further in the study after the telephone interview that collected data on residential history were included in the wire-coding portion of the study if they had an eligible current or former dwelling. The main exposure metric consisted of a TWA summary measure based on the 24-h measurement and the indoor spot measurements taken in multiple residences, if applicable. The measurements were weighted by an estimate of the time spent in each room, made in a separate personal dosimetry study (Friedman *et al*., 1996). The metric was divided into four a-priori cut-points based on the distribution of measurements in the control group. When compared with children who were exposed to magnetic fields < 0.065 μT, the odds ratios for exposure to 0.065–0.099 μT, 0.10–0.199 μT and ≥ 0.2 μT were 1.1 (95% CI, 0.81–1.5; 123 cases), 1.1 (95% CI, 0.83–1.5; 151 cases) and 1.2 (95% CI, 0.86–1.8; 83 cases), respectively, using unmatched analyses. Matched analyses resulted in a slightly higher estimate for the highest exposure category (odds ratio, 1.5; 95% CI, 0.91–2.6; 58 cases). The risk was elevated when the category of magnetic fields of 0.3 μT and above was considered (odds ratio, 1.7; 95% CI, 1.0–2.9; 45 cases), but the trend was not statistically significant, and the odds ratio for magnetic fields of ≥ 0.5 μT was near unity in the matched analysis. There were no significantly elevated risks when exposure during pregnancy was considered. Measurements in the homes that were occupied during pregnancy were made for 257 cases and 239 controls. There was no positive association between wire codes and childhood leukaemia (odds ratio for VHCC versus underground and VLCC, 0.88; 95% CI, 0.48–1.6; 24 cases). [The Working Group noted that the low response rate of the controls was a limitation of this study.]

Hatch *et al.* (2000) conducted a re-analysis of the National Cancer Institute/ Children's Cancer Group study to evaluate internal evidence for selection bias. Certain characteristics of the subjects who did not allow in-home measurements or interviews (partial participants) were compared with those of subjects who did allow a data collector inside their homes (complete participants). The partial participants were found to be more likely to have annual incomes of < $ 20 000 (23% versus 12%), mothers who were unmarried (25% versus 10%), a lower education level (46% versus 38%) and were less likely to live in a single-family home (58% versus 83%) than complete participants. When partial participants were excluded from the analysis of measured fields, the odds ratios for magnetic fields of ≥ 0.3 μT increased from 1.6

(95% CI, 0.98–2.6) to 1.9 (95% CI, 1.1–3.3). When partial participants were excluded from the wire-code analysis, the odds ratios for VHCC (versus UG/VLCC) increased from 1.0 (95% CI, 0.62–1.6) to 1.2 (95% CI, 0.74–2.0). If the non-participants had similar characteristics to partial participants, the National Cancer Institute/Children's Cancer Group study may have overestimated risk estimates due to selection bias. [The Working Group noted that this publication included both complete and partial participants. The risk estimates differed slightly due to small differences in the study populations included and to differences in the variables adjusted for.]

Auvinen *et al*. (2000) carried out an exploratory analysis of the National Cancer Institute/Children's Cancer Group study data using alternative magnetic field exposure metrics. The analysis was restricted to 515 cases of acute lymphoblastic leukaemia and 516 controls who had lived in one home for at least 70% of the time-period of interest. Subjects with Down syndrome were excluded. Measures of the central tendency, peak values, the percentage of time above various thresholds and the short-term variability of the 24-h bedroom measurements were also assessed. A weak positive association was found between acute lymphoblastic leukaemia and measures of the central tendency, particularly when night-time exposure was assessed. For example, when the 30th percentile values of the 24-h measurements were examined, the odds ratios for the highest versus the lowest category (90th% versus < 50th%) were 1.4 (95% CI, 0.87–2.2) for the 24-h measurements and 1.7 (95% CI, 1.1–2.7) for the night-time measurements. Little evidence for any association with peak exposure, thresholds or variability was found.

Kleinerman *et al*. (2000) examined data from the National Cancer Institute/ Children's Cancer Group study in relation to distance from power lines and an exposure index which took into account both distance and relative load for high-voltage and three-phase primary power lines. Most of the subjects (601/816; 74%) had lived more than 40 m from a high-voltage or three-phase primary power line. The odds ratio for living within 14 m of a potentially high-exposure line was 0.79 (95% CI, 0.46–1.3) and that for the highest category of the exposure index (mean magnetic field in homes, 0.213 μT), described above, was 0.98 (95% CI, 0.59–1.6).

Measurements of magnetic fields were included in a population-based case–control study of leukaemia in children under the age of 15 years in Germany. The study area was at first restricted to north-western Germany (i.e. Lower Saxony) (Michaelis *et al*., 1997), but was extended to include the metropolitan area of Berlin (Michaelis *et al*., 1998), before the first part was completed. Patients in whom leukaemia was diagnosed between 1988 and 1993 (for Lower Saxony) or 1991 and 1994 (for Berlin) were identified by the nationwide German Childhood Cancer Registry. In the Lower Saxony part of the study, two controls per case were selected randomly from the files for registration of residents. One control was matched for sex, date of birth and community; a second control was matched only for sex and date of birth, but drawn at random from any community in Lower Saxony, taking the population size of each community into account. In the Berlin part of the study, one control per case matched according to sex,

date of birth and district within the city was randomly selected from the Berlin population registry. Measurements of the magnetic field were also made for patients with tumours of the central nervous system (Schüz *et al*., 2001b), but no controls were selected specifically for this diagnostic group. A total of 176 children with leukaemia, 64 with tumours of the central nervous system and 414 controls participated in the study (Michaelis *et al.*, 1998; Schüz *et al.*, 2001b). The response rates were 62% (176/283) for cases and 45% (414/919) for controls. In both parts of the study, measurements of the magnetic field over 24 h were performed in the child's bedroom and in the living room of the dwelling where the child had lived for longest before the date of diagnosis. Additional spot measurements were made in all dwellings where the child had lived for more than one year. All measurements were made between 1992 and 1996. The main analysis was based on the median magnetic field in the child's bedroom, with 0.2 μT as a cut-point. Post-hoc exposure metrics included the mean of the spot measurements, and the magnetic field during the night (22:00 to 06:00, extracted from the 24-h measurement). The odds ratios were derived from a logistic regression analysis stratified for age, sex and part of Germany (East-Berlin versus West-Berlin and Lower Saxony) and were adjusted for socioeconomic status and degree of urbanization. For the analysis of tumours of the central nervous system, the sample of controls selected for the leukaemia cases was used in unconditional logistic regression models adjusted for age, sex, socioeconomic status and degree of urbanization. Information on a variety of potential confounders was available. The odds ratio for median magnetic fields ≥ 0.2 μT compared with fields of < 0.2 μT was 2.3 (95% CI, 0.8–6.7; 9 exposed cases and 8 exposed controls) for leukaemia and 1.7 (95% CI, 0.3–8.8); 2 exposed cases) for tumours of the central nervous system. The association with leukaemia was more pronounced for children aged four years or younger (odds ratio, 7.1 (95% CI, 1.4–37; 7 cases, 2 controls) and for all children exposed to median magnetic fields ≥ 0.2 μT during the night (odds ratio, 3.8; 95% CI, 1.2–12; 9 cases, 5 controls). No association was seen with spot measurements; spot measurements and 24-h measurements showed a poor agreement. It is also of interest that more of the stronger magnetic fields were caused by low-voltage field sources than by overhead power lines. [The Working Group noted that selection bias is a cause for concern due to the high proportion of non-participants.]

To assess the risk of childhood cancer from exposure to ELF electric and magnetic fields, Dockerty *et al*. (1998) conducted a population-based case–control study in New Zealand. The study base consisted of children under the age of 15 years diagnosed from 1990–1993 with leukaemia or a solid tumour. Children with cancer were identified from the New Zealand Cancer Registry, the New Zealand Children's Cancer Registry or the computerized records of admissions and discharges from public hospitals. The controls were selected at random from national birth records and one control was matched to each case on age (same quarter of the birth year) and sex. Only cases and controls resident in New Zealand and not adopted were included. Altogether, 344 children with cancer were eligible for inclusion in this study, 131 of

whom had leukaemia. Household measurements were made for 115 leukaemia patients and 117 controls, resulting in 113 matched pairs (86%). The response rate among first-choice controls was 69%. Measurements of the magnetic field and the electrical field were conducted over 24 h in two rooms of the dwelling; one was the room in which the child slept at night and one was the room in which the child spent most of his or her day. The two measurements were taken on subsequent days so that the parents had to move the measurement instrument from one room to another. A log sheet was used to record the times and dates on which the instrument was started and moved. Analyses using conditional logistic regression models were performed for thirds of the empirical distributions of the exposure metrics for electric fields and, for magnetic field measurements, for categories 0.1–< 0.2 μT and ≥ 0.2 μT compared with < 0.1 μT. The confounders considered in the analyses included mother's education, maternal smoking during pregnancy, residence of the child on a farm, home ownership status, number of people in the household, residential mobility, mother's marital status and season of the measurement. Risk estimates were presented for a subset of 40 matched pairs for which, two years before the date of diagnosis, both the leukaemia case and the matched control lived in the same house in which the measurements were subsequently made. For leukaemia, the adjusted odds ratios for magnetic fields ≥ 0.2 μT compared with < 0.1 μT were 16 (95% CI, 1.1–224; based on 5 exposed cases and 1 exposed control) for the bedroom measurement and 5.2 (95% CI, 0.9–31; based on 7 exposed cases and 3 exposed controls) for the daytime room measurement. The respective odds ratios for the highest third electric field (≥ 10.75 V/m) compared with the lowest third (< 3.64 V/m) were 2.3 (95% CI, 0.4–13) and 2.5 (95% CI, 0.3–18). Dockerty *et al*. (1999) re-analysed the above data by combining daytime and night-time magnetic fields to produce TWA magnetic fields. The odds ratio for magnetic fields ≥ 0.2 μT decreased to 3.3 (95% CI, 0.5–24) based on the same 40 matched pairs. The analyses of all 113 matched pairs showed no association with exposure to magnetic fields ≥ 0.2 μT (odds ratio, 1.4; 95% CI, 0.3–6.3). [The Working Group noted that risk estimates for leukaemia were presented for only 35% of the matched pairs included in the study.]

McBride *et al*. (1999) conducted a prospective case–control study of childhood leukaemia in five Canadian provinces (Alberta, British Columbia, Manitoba, Quebec and Saskatchewan) from 1990–95. Cases were identified through paediatric oncology treatment centres in each province and provincial cancer registries for all provinces except Quebec. Children under 15 years of age in whom leukaemia had been diagnosed and who resided in census tracts within 100 km of major cities were eligible for the study. A total of 445 potentially eligible cases were identified, and 399 of them were interviewed (90%). In-home measurements were made for 67% of the total eligible cases. The controls were identified from health insurance rolls (and family allowance rolls for the first two years of the study period in Quebec) and were matched by age, sex and area to cases. Of the 526 eligible controls, 399 were interviewed (76%) and in-home measurements were made for 65% of the total. Exposure was assessed by

personal monitoring for 48 h as well as by 24-h stationary measurements in the child's bedroom if the home lived in before diagnosis was still occupied by the child at the date of interview. Wire codes were assigned and outdoor measurements at current and former dwellings (except for apartments more than four storeys high) were made. The personal exposure of subjects in their former dwellings was assessed from outdoor (perimeter) measurements in conjunction with wire codes. The model was based on analyses from currently occupied residences. For children under three years of age, homes occupied for at least three months, and for children over three years of age, homes lived in for six months or more were eligible for exposure assessment. Cases were ascertained retrospectively for one year, and prospectively thereafter; thus, most of the measurements were taken relatively close in time to the diagnosis or reference date. The potential confounding variables that were assessed included outdoor temperature at the time of measurement, family history of cancer, occupational and recreational exposure of parents, exposure to ionizing radiation and socioeconomic factors. The results of personal monitoring gave no indication of a positive association between risk for leukaemia and increasing exposure to magnetic fields, whether based on contemporaneous measures, a measure of estimated exposure two years before the reference date, or estimated lifetime exposure. For the highest exposure category of the contemporary measures (≥ 90th percentile or ≥ 0.27 μT versus < 50th percentile or < 0.08 μT), the unadjusted odds ratio was 0.78 (95% CI, 0.46–1.3), based on 32 exposed cases and 37 exposed controls. Similar results were found when estimated exposure from former residences was included in the exposure assessment. For the 24-h bedroom measurements, the odds ratio for ≥ 90th percentile was 1.3 (95% CI, 0.69–2.3) compared to < 50th percentile. For wire codes, when VHCC was compared with UG and VLCC, the adjusted odds ratio was 1.2 (95% CI, 0.58–2.3), using the residence at the reference date. There was also no association found between childhood leukaemia and measured electric fields. [The Working Group considered that the limitations of this study include relatively low response rates for controls and a higher proportion of controls than of cases who had not moved home since diagnosis.]

Green *et al*. (1999b) carried out a case–control study of childhood leukaemia in the greater Toronto area of Ontario, Canada. Eligible children were under 15 years of age at diagnosis, treated at the Hospital for Sick Children (the only children's hospital in the greater Toronto area) between 1985 and 1993 and still resident in the study catchment area when the study was conducted (1992–95). Patients were identified through a paediatric oncology registry in Ontario. All subjects had to have lived in the study area at the diagnosis or reference date, to ensure comparability in terms of residential stability. A total of 298 children were identified of whom 256 were approached and 203 [68%] interviewed. Controls were selected from a random sample of 10 000 published telephone numbers. A total of 4180 numbers were called and 1133 households were found to have eligible children and be willing to participate. [The number of eligible persons who refused at this stage was not stated.] Of the 1133 potential controls, 645 (two controls per case) were randomly selected and matched

by age and sex. A total of 419 (65%) of the 645 controls approached were interviewed. The assessment of exposure to magnetic fields included spot measurements made in the child's bedroom under normal-power conditions and in two other rooms frequently used by the child, outside measurements around the perimeter of the house, personal monitoring and wire codes. Personal monitoring and in-home measurements were used only if the current residence was occupied before diagnosis or the comparable reference date for the controls. Bedroom measurements were taken for 152 cases [51% of those originally identified] and 300 controls (47% of those approached). The results were analysed using conditional logistic regression and measurements were divided into quartiles according to the distribution among the controls. For bedroom measurements, the adjusted odds ratio for all leukaemias for the highest quartile (≥ 0.13 μT versus < 0.03 μT) was 1.1 (95% CI, 0.31–4.1). Similarly, for the average of interior measurements, the odds ratio was 1.5 (95% CI, 0.44–4.9) for the highest versus lowest quartile. For the exterior measurements, which were taken for a greater number of residences (183 cases and 375 controls), the odds ratios for the second quartile (4.1; 95% CI, 1.3–13 for 0.03–0.07 μT) and for the fourth quartile (3.5; 95% CI, 1.1–11 for ≥ 0.15 μT) were elevated compared with the lowest quartile. There was no association between wire-code and leukaemia incidence. The results for the personal exposure monitoring, based on only 88 cases (34%) and 113 controls (18%) were published separately (Green *et al.*, 1999a). There was a significantly increased risk for all childhood leukaemias for the third (0.07 μT–0.14 μT) and fourth (≥ 0.14 μT) quartiles of magnetic field exposure, compared with the lowest quartile (< 0.03 μT). The odds ratios were 4.0 (95% CI, 1.1–14) and 4.5 (95% CI, 1.3–16) for the third and fourth quartile, respectively, after adjustment for average power consumption, family income, residential mobility, exposure of the child to chemicals and birth order. The odds ratios for electric fields measured by personal dosimetry were mostly below unity. [The Working Group noted that the limitations of the study include the low response rates, especially for the personal monitoring part of the study, and that measurements were taken many years after the time period of interest. The use of published telephone listings raises concern about the comparability of cases and controls.]

The United Kingdom Childhood Cancer Study (UKCCS) was a population-based case–control study covering the whole of England, Wales and Scotland (UK Childhood Cancer Study Investigators, 1999). The study population was defined as children under the age of 15, registered with one of the Family Health Service Authorities (England and Wales) or with one of the Health Boards (Scotland). The prospective collection of cases with a pathologically confirmed malignant disease began in 1992 (except in Scotland where it began in 1991) and ended in 1994 (except in England and Wales, where cases with leukaemia were collected throughout 1996 and cases with non-Hodgkin lymphoma throughout 1995). For each case, two controls, matched for sex and date of birth, were selected randomly from the list of the same Family Health Service Authorities or Health Board as the case. For the study of

electric and magnetic fields, only one control per case was chosen. At first, the family of the control with the lower identification number of the two controls was approached and, in case of non-participation or ineligibility, a second control family was chosen. Case and control families were ineligible for the electric and magnetic field part of the study if they had moved house during the year before diagnosis or lived in a mobile home. A total of 3838 cases (87% of all eligible cases in the UK Childhood Cancer Study) were included, and at least one of the parents was interviewed. A total of 7629 controls were included and the participation rate was 64%. Measurements were made for 2423 cases and 2416 controls; 2226 matched pairs (50% of all cases [37% of half of the controls]) were available for analysis. Of the 2226 cases, 1073 had leukaemia, 387 had cancer of the central nervous system and 766 had another malignant disease. The protocol for exposure assessment was specifically designed to estimate the average magnetic fields to which the subjects had been exposed in the year before diagnosis and measurements were made in the homes of all participants during the first phase of exposure assessment. These first-phase measurements comprised a 1.5-h stationary measurement in the centre of the main family room and three spot measurements at different places in the child's bedroom, which were repeated after the 1.5-h measurement. During the household visits, the parents were asked about potential sources of exposure, e.g. night storage heaters, and about the amounts of time the child spent in his or her room and at school. An exposure assessment was carried out in the child's school where relevant. In the second phase of exposure assessment, a measurement over a period of 48 h was conducted in homes where the first measurement had indicated magnetic fields ≥ 0.1 μT, where a potential source of exposure had been identified during the first visit or where an external source of exposure had been reported on a questionnaire that had been completed by the regional electricity companies. If the potential field source was assumed to have a seasonal variability, the dwelling was revisited during the winter months. The dwellings of the families of matched cases or controls where there were potential sources of exposure were also revisited in the second phase. An algorithm was developed to calculate the TWA exposure to magnetic fields on an individual basis, including the magnetic field strengths measured in the bedroom, in other rooms of the dwelling and at school, but with different weightings for each child according to the amount of time he or she had spent in each place. For participants for whom only first-phase measurements had been made, exposure in the bedroom was estimated from the spot measurements and exposure outside the bedroom was estimated from the 1.5-h measurement made in the main family room. For participants for whom long-term measurements had been made, exposure in the bedroom was estimated from the 48-h measurement and exposure outside the bedroom from the 1.5-h measurement conducted during the first visit. To allow for changes in line-loading and circuit configuration between the year of diagnosis and the time of measurement, the exposure measurements were adjusted to take into account calculated historical magnetic fields. Exposure was divided into four groups (< 0.1 μT, 0.1–< 0.2 μT, 0.2–< 0.4 μT and ≥ 0.4 μT) and into three

categories with cut-points at 0.1 μT and 0.2 μT, respectively. Additional adjustments were performed for a census-derived deprivation index based on unemployment, overcrowding and car ownership in the appropriate district. The odds ratios were presented separately for leukaemia, cancers of the central nervous system, other malignant diseases and all cancers combined. At magnetic fields ≥ 0.2 μT, all the adjusted odds ratios were below unity (leukaemia, odds ratio, 0.90 (95% CI, 0.49–1.6), cancer of the central nervous system, odds ratio, 0.46 (95% CI, 0.11–1.9), other types of cancer, odds ratio, 0.97 (95% CI, 0.46–2.1), all cancers combined, odds ratio, 0.87 (95% CI, 0.56–1.4)). At ≥ 0.4 μT, the odds ratio for leukaemia was slightly elevated (1.7; 95% CI, 0.40–7.1), based on five exposed cases and three exposed controls. No association with magnetic fields of ≥ 0.4 μT was seen for cancer of the central nervous system (no exposed cases) or other malignant diseases (odds ratio, 0.71; 95% CI, 0.16–3.2; three exposed cases). For the intermediate category 0.2–< 0.4 μT, all odds ratios were below unity or, in the case of other malignant diseases, very close to unity (leukaemia, odds ratio, 0.78 (95% CI, 0.40–1.5), cancer of the central nervous system, odds ratio, 0.70 (95% CI, 0.16–3.2), other malignant disease, odds ratio, 1.1 (95% CI, 0.45–2.6)). Adjustment for deprivation index had only a small effect on the risks and risk did not vary according to age. [The Working Group considered that the main limitation of this study was the low proportion of subjects for whom fields were measured.]

In a second approach, the study examined distance from external sources of electric and magnetic fields (UK Childhood Cancer Study Investigators, 2000a). These data were available for nearly 90% of the children eligible for the study of electric and magnetic fields. Separate odds ratios were calculated for different types of overhead power line (11- and 20-kV, 33-kV, 66-kV, 132-kV, 275-kV and 400-kV) and for different types of underground high-voltage cable (33-kV, 132-kV and 275-kV), substations and low-voltage circuits. The only association seen was between leukaemia and 66-kV overhead power lines (odds ratio, 3.2; 95% CI, 1.0–9.7; 5 cases), although associations with other sources of field, including stronger ones, were close to unity. The magnetic fields associated with power lines were also calculated for all dwellings on the basis of line-load data for the period of interest. For magnetic fields of ≥ 0.4 μT, the odds ratio was decreased for leukaemia (0.27; 95% CI, 0.03–2.2), but only one case and eight controls were classified as being exposed. No excess risk for any type of malignancy was seen with exposure to magnetic fields ≥ 0.2 μT.

Bianchi *et al*. (2000) conducted a small case–control study in Italy. The study areas were the municipalities within the Province of Varese that were crossed by high-voltage power lines. A total of 103 children under the age of 15 years diagnosed with leukaemia between 1976 and 1992 were identified by the Lombardy Cancer Registry and four healthy controls per case were selected randomly from the 1996 lists of Health Service Archives. A total of 101 cases and 412 controls were available for analysis. The average magnetic fields for subjects living within 150 m of a power line were calculated from data on the power load for the year 1998. In addition, spot measurements at the entrance of the dwelling were conducted in a validation study.

Odds ratios obtained from logistic regression analysis stratified for age and sex, revealed considerable increases in leukaemia risk from exposure to magnetic fields in the ranges 0.001–0.1 μT (odds ratio, 3.3; 95% CI, 1.1–9.7, 6 cases) and > 0.1 μT (odds ratio, 4.5; 95% CI, 0.88–23, 3 cases), compared to exposure to fields < 0.001 μT (92 cases). [The Working Group noted that current data on power load were used to estimate historical magnetic fields up to 22 years in the past. The highest exposure group was defined at a very low cut-point (> 0.1 μT) and even then comprised only a few subjects. Furthermore, cases and controls were enrolled from two different recruitment periods.]

Schüz *et al*. (2001a) reported the results of a large-scale population-based case–control study covering the whole of the former West Germany. A total of 514 patients with acute leukaemia aged less than 15 years were identified from the German Childhood Cancer Registry from 1990–94, and 1301 controls from population registration files were included. Measurements of magnetic fields were made in 1997–99. [Overall participation rates were 51% among cases and 41% among controls]. Of those families who were asked for permission to conduct measurements, 66% (520/783) responded. The exposure assessment was similar to that of the first German study (Michaelis *et al*., 1998; see above), except that spot measurements were conducted only to identify the source of strong magnetic fields and were not part of the risk analysis. The main exposure metrics were the median magnetic field over 24 h and the median magnetic field during the night. Odds ratios were calculated using logistic regression models adjusted for sex, age, year of birth, social class and degree of urbanization. The odds ratio for 24-h median magnetic fields ≥ 0.2 μT was 1.6 (95% CI, 0.65–3.7; 9 exposed cases and 18 exposed controls). An elevated risk for leukaemia was observed for night-time exposure with an odds ratio of 3.2 (95% CI, 1.3–7.8; 12 exposed cases and 12 exposed controls). At a cut-point of ≥ 0.4 μT, the odds ratio for median magnetic fields increased to 5.8 (95% CI, 0.78–43), but was based on only three exposed cases and three exposed controls. Odds ratios were altered only slightly when the analyses were restricted to residentially stable children. The association was strongest for children aged four years or younger. Two exposed children with Down syndrome had median and night-time exposure > 0.2 μT. The exclusion of children with Down syndrome from the analyses led to a decrease in the odds ratio at ≥ 0.2 μT to 1.3 (95% CI, 0.49–3.2) (7 exposed cases) for median magnetic fields and to 2.8 (95% CI, 1.1–7.0) (10 exposed cases) for night-time exposure, the increase in the latter was still statistically significant. [The Working Group noted that the study had two limitations, the low participation rate and the very long time lag between date of diagnosis and date of measurement.]

A pooled analysis of the two German studies (Michaelis *et al*., 1998; Schüz *et al*., 2001a) resulted in an increase in the odds ratios for leukaemia in children exposed to 24-h median magnetic fields ≥ 0.4 μT to 3.5 (95% CI, 1.0–12; 7 cases). No associations were seen for the intermediate exposure categories of 0.1–< 0.2 μT (odds ratio, 1.1; 95% CI, 0.73–1.6; 43 cases) and 0.2–< 0.4 μT (odds ratio, 1.2; 95% CI, 0.55–2.6;

11 cases), compared with the baseline < 0.1 μT (629 cases). A dose–response relationship was observed for median magnetic fields during the night, with respective odds ratios of 1.3 (95% CI, 0.90–2.0; 44 cases), 2.4 (95% CI, 1.1–5.4; 14 cases) and 4.3 (95% CI, 1.3–15; 7 cases) for the exposure categories 0.1–< 0.2 μT, 0.2–< 0.4 μT and ≥ 0.4 μT, respectively (*p* value for trend < 0.01) (Schüz *et al*., 2001a).

The study also examined exposure to $16\,^2/_3$-Hz magnetic fields, which is the frequency used by the German railway system (Schüz *et al*., 2001c). Magnetic fields ≥ 0.2 μT at this frequency were measured in less than 1% of all dwellings. Considering this additional exposure in the main analysis changed the results only marginally, thus, neglecting magnetic fields at this frequency is not likely to affect studies of residential electric and magnetic fields.

(*d*) *Pooled analyses*

(i) Ahlbom *et al*. (2000) reported a pooled analysis of studies that examined the relation between childhood leukaemia and residential magnetic fields (Table 22). They included all studies except one (London *et al*., 1991) in which long-term indoor measurements had been reported and that were completed before 2000 (Linet *et al*., 1997; Michaelis *et al*., 1998; Dockerty *et al*., 1998; 1999; McBride *et al*., 1999; UK Childhood Cancer Study Investigators, 1999) and all studies that reported calculations of historical exposure to ELF magnetic fields (Feychting & Ahlbom, 1993; Olsen *et al*., 1993; Verkasalo *et al*., 1993; Tynes & Haldorsen, 1997). The analysis strategy was defined *a priori*. The greatest emphasis was placed on the geometric mean of the child's exposure measured in the bedroom in the most recent home inhabited before or at diagnosis. Exposure was categorized into the groups < 0.1 μT, 0.1–< 0.2 μT, 0.2–< 0.4 μT and ≥ 0.4 μT. The potential effect modifiers that were considered in an additional analysis included type of house, residential mobility, social group (or mother's education or family income), degree of urbanization and exposure to car exhaust. The study population comprised 3247 children with leukaemia, of whom 2704 had acute lymphoblastic leukaemia, and 10 400 controls, all under the age of 15 years. Due to the study protocol described above, the results for the single studies within this pooled analysis sometimes differed from the results originally reported for the same study. These differences were greatest for the US study (Linet *et al*., 1997), the Canadian study (McBride *et al*., 1999) and the United Kingdom study (UK Childhood Cancer Study Investigators, 1999). The pooled analysis modified the data of Linet *et al*. (1997) as follows: homes in which 24-h measurements had not been made were excluded; exposure measured in the year prior to diagnosis, rather than five years immediately prior to diagnosis were used, and arithmetic means were replaced by geometric means. The changes to the original Canadian results (McBride *et al*., 1999) made for the pooled analysis meant that exposure assessments from fixed-location in-home measurements were used instead of measures of exposure recorded with personal dosimeters. The original United Kingdom results (UK Childhood Cancer Study Investigators, 1999) modified for the pooled analysis used the geometric mean from the 1.5/48-h

Table 22. Pooled analysis of total leukaemia in children

Type of study	0.1–< 0.2 μT	0.2–< 0.4 μT	≥ 0.4 μT	O	E	Continuous analysis
Measurement studies						
Canada (McBride *et al.*, 1999)	1.3 (0.84–2.0)	1.4 (0.78–2.5)	1.6 (0.65–3.7)	13	10.3	1.2 (0.96–1.5)
Germany (Michaelis *et al.*, 1998)	1.2 (0.58–2.6)	1.7 (0.48–5.8)	2.0 (0.26–15)	2	0.9	1.3 (0.76–2.3)
New Zealand (Dockerty *et al.*, 1998, 1999)	0.67 (0.20–2.2)	4 cases/0 controls	0 cases/0 controls	0	0	1.4 (0.40–4.6)
United Kingdom (UKCCSI, 1999)	0.84 (0.57–1.2)	0.98 (0.50–1.9)	1.0 (0.30–3.4)	4	4.4	0.93 (0.69–1.3)
USA (Linet *et al.*, 1997)	1.1 (0.81–1.5)	1.0 (0.65–1.6)	3.4 (1.2–9.5)	17	4.7	1.3 (1.0–1.7)
Calculated field studies						
Denmark (Olsen *et al.*, 1993)	2.7 (0.24–31)	0 cases/8 controls	2 cases/0 controls	2	0	1.5 (0.85–2.7)
Finland (Verkasalo *et al.*, 1993)	0 cases/19 controls	4.1 (0.48–35)	6.2 (0.68–57)	1	0.2	1.2 (0.79–1.7)
Norway (Tynes & Haldorsen, 1997)	1.8 (0.65–4.7)	1.1 (0.21–5.2)	0 cases/10 controls	0	2.7	0.78 (0.50–1.2)
Sweden (Feychting & Ahlbom, 1993)	1.8 (0.48–6.4)	0.57 (0.07–4.7)	3.7 (1.2–11.4)	5	1.5	1.3 (0.98–1.7)
Summary						
Measurement studies	1.1 (0.86–1.3)	1.2 (0.85–1.5)	1.9 (1.1–3.2)	36	20.1	1.2 (1.0–1.3)
Calculated field studies	1.6 (0.77–3.3)	0.79 (0.27–2.3)	2.1 (0.93–4.9)	8	4.4	1.1 (0.94–1.3)
All studies	1.1 (0.89–1.3)	1.1 (0.84–1.5)	2.0 (1.3–3.1)	44	24.2	1.2 (1.0–1.3)

From Ahlbom *et al*. (2000)

The results of the pooled analysis show relative risks (95% CI) by exposure level and with exposure as continuous variable (relative risk per 0.2 μT) with adjustment for age, sex and socioeconomic status (measurement studies) and residence (in East or West Germany). The reference level is < 0.1 μT. Observed (O) and expected (E) case numbers at ≥ 0.4 μT are shown, with expected numbers given by modelling the probability of membership of each exposure category based on distribution of controls including covariates.

UKCCSI, UK Childhood Cancer Study Investigators

measurements rather than the TWA of the measurement protocol. The investigators of the Finnish cohort study (Verkasalo *et al*., 1993) provided a sample of 1027 controls drawn from the cohort.

To estimate a summary relative risk across centres in this pooled analysis, a logistic regression model was applied to the raw data, with study centres represented as effect modifiers. This was performed separately for measurement studies and studies of calculated fields, but also across all studies. Across the measurement studies, the summary relative risk was estimated at 1.9 (95% CI, 1.1–3.2) in the highest exposure category (≥ 0.4 μT). The two intermediate categories had relative risks close to unity (0.1–< 0.2 μT: relative risk, 1.1; 95% CI, 0.86–1.3; 0.2–< 0.4 μT: relative risk, 1.2; 95% CI, 0.85–1.5). The corresponding summary relative risks for the studies of calculated fields were 1.6 (95% CI, 0.77–3.3) in the category 0.1–< 0.2 μT, 0.79 (95% CI, 0.27–2.3) in the category 0.2–< 0.4 μT, and 2.1 (95% CI, 0.93–4.9) in the category ≥ 0.4 μT. The summary relative risks across all studies were also close to unity (0.1–< 0.2 μT: relative risk, 1.1; 95% CI, 0.89–1.3; 0.2–< 0.4 μT: relative risk, 1.1; 95% CI, 0.84–1.5), but in the highest category (≥ 0.4 μT), the summary relative risk was 2.0 (95% CI, 1.3–3.1) with a respective p value < 0.01. A similar analysis was conducted on continuous exposure, and the resulting relative risk per 0.2 μT interval was 1.2 (95% CI, 1.0–1.3). A homogeneity test based on the continuous analysis across all nine centres revealed that the variation in point estimates between the studies was not larger than would be expected from random variability. Subsequent sensitivity analysis confirmed that the observed association between leukaemia and stronger magnetic fields was not due to the choice of exposure metric (geometric mean) or the definition of cut-points, and was not strongly influenced by any of the studies. Consideration of potential confounders did not materially affect the risk estimates. The summary relative risks for acute lymphoblastic leukaemia only were similar to those obtained for total leukaemia. While the relative risks for the intermediate exposure categories were 1.1 (95% CI, 0.88–1.3) for the category 0.1–< 0.2 μT and 1.1 (95% CI, 0.84–1.5) for the 0.2–< 0.4 μT category, the relative risk for the highest exposure category (≥ 0.4 μT) showed a twofold increase (2.1; 95% CI, 1.3–3.3).

A comparison was made in the pooled analysis between the number of observed cases and the number of expected cases under the null hypothesis at ≥ 0.4 μT. In three studies, no excess leukaemia cases were observed; these were the United Kingdom study (4 observed, 4.4 expected cases), the Norwegian study (0 observed, 2.7 expected) and the New Zealand study (0 observed, 0 expected). The summary numbers across all studies were 44 observed cases compared with 24.2 expected cases.

Another finding of this pooled analysis related to the so-called wire code paradox. In earlier reviews, it had been observed that there was a stronger association between surrogates for exposure to ELF electric and magnetic fields and leukaemia risk than between direct measurements and leukaemia risk. The new studies did not support this. The summary relative risk of the US (Linet *et al*., 1997) and Canadian studies

(McBride *et al*., 1999) combined for the highest wire-code category was 1.2 (95% CI, 0.82–1.9) which was lower than that in the measurement or calculated field studies.

(ii) Greenland *et al*. (2000) reported a pooled analysis of 16 studies of childhood leukaemia and residential magnetic fields, based on either magnetic field measurements or wire codes. In contrast to the pooled analysis by Ahlbom *et al*. (2000), this analysis also included studies that relied only on wire codes for exposure assessment as well as some of the earlier studies which were smaller and less methodologically sound than more recent studies. The additional studies not included by Ahlbom *et al*. (2000) were those by Wertheimer and Leeper (1979), Fulton *et al*. (1980), Tomenius (1986), Savitz *et al*. (1988), London *et al*. (1991), Coghill *et al*. (1996), Fajardo-Gutiérrez *et al*. (1997) and Green *et al*. (1999a,b). The study carried out in the United Kingdom (UK Childhood Cancer Study Investigators, 1999) was not included in this pooled analysis, and from the study by Green *et al*. (1999a,b), only wire-code data were included. Eight of the studies (Coghill *et al.*, 1996; Linet *et al.*, 1997; London *et al.*, 1991; Michaelis *et al.*, 1998; Savitz *et al.*, 1988; Tomenius, 1986; Dockerty *et al.*, 1998; McBride *et al.*, 1999) provided some direct measurements of magnetic fields; four studies from the Nordic countries (Feychting & Ahlbom, 1993, Sweden; Olsen *et al.*, 1993, Denmark; Verkasalo *et al.*, 1993, Finland; Tynes & Haldorsen, 1997, Norway) were based upon calculated historical fields. Most studies provided multiple measurements. The a-priori measurement chosen for this pooled analysis was the best approximation of TWA exposure up to three months before diagnosis. Magnetic field strengths were categorized into groups ≤ 0.1 μT, > 0.1–≤ 0.2 μT, > 0.2–≤ 0.3 μT and > 0.3 μT. Data were analysed using maximum likelihood logistic regression and tabular methods. For the wire code analyses, the referent group consisted of low wire codes (underground [UG], VLCC and ordinary low current [OLCC] combined). For the measurement analysis, the combined results of the 12 studies gave relative risks of 1.01 (95% CI, 0.84–1.2), 1.06 (95% CI, 0.78–1.4) and 1.7 (95% CI, 1.2–2.3) for > 0.1–≤ 0.2, > 0.2–≤ 0.3 and > 0.3 μT compared with < 0.1 μT, respectively, using Mantel-Haenszel summary estimates and adjusting for study, age and sex. Restricting the studies to those with complete covariate data resulted in very similar estimates. The relative risks were 1.01 (95% CI, 0.82–1.3), 0.94 (95% CI, 0.65–1.4) and 2.1 (95% CI, 1.4–3.0) for > 0.1–≤ 0.2, > 0.2–≤ 0.3 and > 0.3 μT, respectively, using Mantel-Haenszel summary estimates, and adjusting for age, sex and socioeconomic variables. For the analysis of wire codes, summary estimates were not given for all of the studies, because of a great deal of heterogeneity within the study results, ranging in relative risks for VHCC of < 1 in three studies to > 2 in three studies (homogeneity $p = 0.005$). Eliminating the two earliest studies, which had extreme results, the summary relative risks were 1.02 (95% CI, 0.87–1.2) and 1.5 (95% CI, 1.2–1.9) for OHCC and VHCC, respectively, based on six studies with wire code data. Covariate adjustment had little effect on these results. As with the pooled analysis of Ahlbom *et al.* (2000), the 'wire-code paradox' was not evident, since measured fields showed stronger associations with childhood leukaemia than did wire codes. The two pooled analyses reached similar conclusions.

2.2.2 *Exposure to ELF electric and magnetic fields from electrical appliances* (Table 23)

Seven studies have examined the relationship between use of household electrical appliances and all childhood cancers, childhood leukaemia or tumours of the brain and nervous system. The first study, as described above (Savitz *et al*., 1988), was conducted in Denver, CO, USA (Savitz *et al*., 1990). A total of 252 children with cancer, identified through a tumour registry and area hospitals, and 222 controls, identified by random-digit dialling, were interviewed. The response rates were 70.8% for cases (252/356 eligible cases) and 79.9% for eligible controls (222/278). Maternal use of appliances during pregnancy and the use of appliances by the children in the study were assessed. Results for four appliances were presented: electric blankets, heated water beds, bedside electric clocks and bed-heating pads. For ever-use of electric blankets during pregnancy, the adjusted odds ratio was 1.7 (95% CI, 0.8–3.6; 13 exposed cases) for leukaemia and 2.5 (95% CI, 1.1–5.5; 11 exposed cases) for brain cancer in children. Slightly stronger effects were noted when use during the first trimester of pregnancy was considered (leukaemia, odds ratio, 2.3 (95% CI, 1.0–5.8), 9 cases; brain cancer, odds ratio, 4.0 (95% CI, 1.6–9.9), 9 cases) and for more hours of use, i.e. > 8 h versus < 8 h (leukaemia, odds ratio, 11 (95% CI, 1.8–67), 4 cases; brain cancer, odds ratio, 4.6 (95% CI, 0.5–39), 1 case). No significant associations were found for childhood use of electric appliances. Electric blankets had been used in childhood by only 13 cancer cases and eight control children; the odds ratio was 1.5 (95% CI, 0.5–5.1) for leukaemia and 1.2 (95% CI, 0.3–5.7) for brain cancer. Odds ratios for use of electrically heated water beds and hair dryers were mostly below one and those for bedside electric clocks were slightly elevated, but not significant (odds ratio for total cancer, 1.3; 95% CI, 0.8–2.2). [The Working Group noted that a potential problem of the study, in addition to the possible selection bias described previously, is that parents of cases and controls were interviewed many years after the time period of interest.]

The second study to include use of electric appliances as part of assessment of exposure to magnetic fields was conducted in Los Angeles, CA, USA (London *et al*., 1991, 1993). Two hundred and thirty-two children with leukaemia and 232 matched controls were interviewed. There was no indication of any important associations between maternal use of electrical appliances during pregnancy and risk for childhood leukaemia, but there were several significantly elevated odds ratios for use of appliances during childhood. Exposure during childhood was defined as use at least once per week in comparison to no use of the appliance. For black-and-white televisions, the odds ratio was 1.5 (95% CI, 1.0–2.2); that for use of hair dryers was 2.8 (95% CI, 1.4–6.3). Elevations in risk were also seen for use of electric dial clocks (odds ratio, 1.9; 95% CI, 0.97–3.8), curling irons (odds ratio, 6.0; 95% CI, 0.72–105), electric blankets (odds ratio, 7.0; 95% CI, 0.86–122) and video games (odds ratio, 1.6; 95% CI, 0.8–3.3). [The Working Group noted that because of the small numbers of appliance users, no attempt had been made to define high- or low-exposure groups.]

Table 23. Case–control studies of childhood cancer in relation to use of electrical appliances

Reference, area	Study size and cancer site	Exposure	No. of cases	Risk estimates: odds ratios (95% CI)	Comment
Savitz *et al*. (1990), Denver, CO, USA	252 cases, 222 controls, aged 0–14 years, diagnosed 1976–83	**Electric blankets**			Unadjusted odds ratios. Evidence of effect modification by income; no consistent evidence for increased risks with water beds, bedside electric clocks or heating pads; study vulnerable to selection bias due to differential residential restrictions placed on cases versus controls
	All cancers (233 cases)	Prenatal use	38	1.1 (0.7–1.8)	
	(244 cases)	Postnatal use	13	1.5 (0.6–3.4)	
	Leukaemia (70 cases)	Prenatal use	13	1.3 (0.7–2.6)	
	(73 cases)	Postnatal use	4	1.5 (0.5–5.1)	
	Brain cancer (45 cases)	Prenatal use	11	1.8 (0.9–4.0)	
	(47 cases)	Postnatal use	2	1.2 (0.3–5.7)	
London *et al*. (1991), Los Angeles, CA, USA	232 cases of leukaemia, 232 controls, aged 0–10 years, diagnosed 1980–87	**Electric blankets**			No evaluation by frequency and/or duration of use of appliances; assessment of use made many years after etiological time-period
		Prenatal use	23	1.2 (0.66–2.3)	
		Postnatal use	7	7.0 (0.86–122)	
		Water beds			
		Prenatal use	14	0.67 (0.34–1.3)	
		Postnatal use	12	1.0 (0.45–2.3)	
		Television (black and white)			
		Postnatal use	64	1.5 (1.0–2.2)	
		Hair dryer			
		Postnatal use	31	2.8 (1.4–6.3)	
McCredie *et al*. (1994), Australia	82 cases of brain tumour, 164 controls, aged 0–14 years, diagnosed 1985–89	**Postnatal**			No assessment of dose–response and only two appliances considered
		Electric blankets	6	0.4 (0.2–1.2)	
		Water beds	1	0.2 (0–1.5)	

Table 23 (contd)

Reference, area	Study size and cancer site	Exposure	No. of cases	Risk estimates: odds ratios (95% CI)	Comment
Preston-Martin *et al*. (1996a), Los Angeles, CA	298 cases of brain tumour, 298 controls, aged 0–19 years, diagnosed 1984–91	**Electric blankets**			Slightly, non-significantly elevated risks for electric heat: prenatal (odds ratio, 1.6; 95% CI, 0.8–3.0), postnatal (odds ratio, 1.3; 95% CI, 0.7–2.4); some indication of higher risks among cases diagnosed in earlier time-period, suggesting possible control selection bias
		Prenatal use	20	1.2 (0.6–2.2)	
		Postnatal use	11	1.2 (0.5–3.0)	
		Water beds			
		Prenatal use	23	2.1 (1.0–4.2)	
		Postnatal use	8	2.0 (0.6–6.8)	
		Television (black and white)			
		Postnatal use	20	0.7 (0.4–1.4)	
		Hair dryer			
		Postnatal use	55	1.2 (0.7–2.1)	
Gurney *et al*. (1996), Seattle, WA	133 cases of brain tumour, 270 controls; aged 0–19 years, diagnosed 1984–90	Electric blankets			Some elevated odds ratios for childhood use of digital clocks, black-and-white television, incubators, and baby monitors; no association for electric heat
		Prenatal use	20	0.9 (0.5–1.6)	
		Postnatal use	6	0.5 (0.2–1.4)	
		Water beds			
		Prenatal use	20	0.7 (0.4–1.3)	
		Postnatal use	8	0.8 (0.3–1.9)	

Table 23 (contd)

Reference, area	Study size and cancer site	Exposure	No. of cases	Risk estimates: odds ratios (95% CI)	Comment
Hatch *et al*. (1998), 9 mid-western and mid-Atlantic states	651 cases of acute lymphoblastic leukaemia, 651 matched controls, aged 0–14 years, diagnosed 1989–93	**Electric blankets**			Dose–response trends by frequency and duration of use of appliances were not apparent; results may have been affected by recall bias
		Prenatal use	91	1.6 (1.1–2.3)	
		Postnatal use	45	2.8 (1.5–5.0)	
		Sewing machines			
		Prenatal use	198	0.76 (0.59–0.98)	
		Television (< 4 ft vs ≥ 6 ft [1.2 vs ≥ 1.8 m] from TV)			
		Prenatal use	17	1.9 (0.79–4.5)	
		Postnatal use	166	1.6 (1.1–2.4)	
		≥ 6 h vs < 2 h/day			
		Postnatal use	178	2.4 (1.5–3.8)	
		Hair dryer			
		Postnatal use	266	1.6 (1.2–2.1)	
Dockerty *et al*. (1998), New Zealand	303 cancer cases, 303 controls, aged 0–14 years, diagnosed 1990–93				Adjusted odds ratios. No assessment of dose–response trends by amount of use
		Electric blankets			
	Leukaemia (121 cases)	Prenatal use	30	0.8 (0.4–1.6)	
		Postnatal use	17	2.2 (0.7–6.4)	
	Central nervous system cancer (58 cases)	Prenatal use	18	1.6 (0.6–4.3)	
		Postnatal use	8	1.6 (0.4–7.1)	
	Other solid tumours (124 cases)	Prenatal use	35	1.8 (0.9–3.5)	
		Postnatal use	26	2.4 (1.0–6.1)	

TV, television

McCredie *et al*. (1994) included an assessment of use of electric blankets and water beds in a study of childhood brain tumours (ICD-9, 191, 192) in New South Wales, Australia. A total of 97 eligible children aged 0–14 years and diagnosed with a brain tumour between 1985 and 1989, were identified from a population-based cancer registry for the areas of Sydney, Wollongong and Newcastle. Eighty-two (85%) of the mothers of children with cancer were interviewed. Potential control mothers were identified from electoral rolls in a two-phase selection process. Sixty per cent (400/672) of the mothers of eligible control children agreed to be interviewed and 164 of them were interviewed. Childhood use of electric blankets and water beds were the only potential sources of exposure to magnetic field assessed in this study. The odds ratio was 0.4 (95% CI, 0.2–1.2) for regular use of an electric blanket and 0.2 (95% CI, 0–1.5) for regular use of a water bed.

Preston-Martin *et al*. (1996b) studied the use of electrical appliances in relation to risk for childhood brain tumours (ICD-9 191, 192). Children aged 0–19 years, with brain tumours diagnosed between 1984 and 1991 were identified from three population-based cancer registries on the West Coast of the USA (Los Angeles County, five counties of the San Francisco area and 13 counties in Washington State including Seattle) for the years 1984–91. Controls were identified by random-digit dialling and were frequency-matched by age and sex to the case group. Mothers of a total of 540/739 cases (73%) and 801/1079 controls (74%) were interviewed about their use of electric blankets and electrically heated water beds during pregnancy and about use by the child after birth. No association of brain tumours with in-utero exposure to electric blankets (odds ratio, 0.9; 95% CI, 0.6–1.2) or use by the child (odds ratio, 1.0; 95% CI, 0.6–1.7) was found. There was also no effect of in-utero exposure resulting from use of water beds by the mother (odds ratio, 0.9; 95% CI, 0.6–1.3) or of use of water beds by children (odds ratio, 1.2; 95% CI, 0.7–2.0). When the analysis was restricted to the Los Angeles county (Preston-Martin *et al.* (1996a), the odds ratios for electric blankets were 1.2 (95% CI, 0.6–2.2) and 1.2 (95% CI, 0.5–3.0) for in-utero and postnatal exposure, respectively, and for water beds, the odds ratios were 2.1 (95% CI, 1.0–4.2) and 2.0 (95% CI, 0.6–6.8), respectively.

In a subset of the study population from the Seattle area (98 cases and 208 controls), Gurney *et al*. (1996) reported small, but non-significant elevations in risk for brain tumours associated with childhood use of portable black-and-white televisions (odds ratio, 1.6; 95% CI, 0.6–3.9), bedside digital clocks (odds ratio, 1.8; 95% CI, 0.9–3.3) and incubators (odds ratio, 1.5; 95% CI, 0.8–3.1), but no elevations in risk were associated with maternal use of appliances during pregnancy. In another subset of 133 cases and 270 controls, no association was seen for prenatal or postnatal exposure to electric blankets or water beds.

Hatch *et al*. (1998) examined both prenatal and postnatal use of appliances in the National Cancer Institute/Children's Cancer Group Study in the USA as described above. Interview data on the use of electrical appliances was available for 788 children, aged 0–14 years, with acute lymphoblastic leukaemia diagnosed between 1989 and 1993

[88% response] and 699 controls [64% response], providing 651 matched pairs. The use of several appliances during the prenatal period was significantly associated with the occurrence of acute lymphoblastic leukaemia, but there was no evidence of a dose–response effect. For ever- versus never-use by the mother during pregnancy, the odds ratios for the offspring were 1.6 (95% CI, 1.1–2.3) for electric blankets, 1.5 (95% CI, 1.0–2.1) for bed-heating pads, 1.4 (95% CI, 1.0–2.0) for humidifiers and 0.76 (95% CI, 0.59–0.98) for sewing machines. Some significant associations with childhood leukaemia were also found with use of electrical appliances during childhood, based on the mother's report. Ever-use of an electric blanket prior to the reference date was associated with an odds ratio of 2.8 (95% CI, 1.5–5.0), but the highest risk was found for the shortest duration of use in years (odds ratio for < 1 year of use, 5.5; 95% CI, 1.1–26). Similarly, the odds ratio for ever-use of a hair dryer was 1.6 (95% CI, 1.2–2.1), but the highest risk was for children who had used one hair dryer for less than one year (odds ratio, 2.5; 95% CI, 1.3–4.9). There was some suggestion of effects for video arcade games (odds ratio, 1.7; 95% CI, 1.2–2.3) and video games connected to televisions (odds ratio, 1.9; 95% CI, 1.4–2.7), but no indication of increased risks associated with use of a personal computer (odds ratio, 1.2; 95% CI, 0.83–1.7). The risk increased with increasing amount of time spent watching television (odds ratio for ≥ 6 h per day versus < 2 h per day, 2.4; 95% CI, 1.5–3.8), but these effects were seen regardless of the reported distance that the child sat from the television.

Dockerty *et al*. (1998) included assessment of exposure to electrical appliances in a nationwide study of childhood cancer in New Zealand (described above) (303 cases, 303 controls). There was little evidence for any relationship between maternal use of electrical appliances in pregnancy and childhood cancer. The odds ratios for use of electric blankets were 0.8 (95% CI, 0.4–1.6) for leukaemia, 1.6 (95% CI, 0.6–4.3) for cancers of the central nervous system and 1.8 (95% CI, 0.9–3.5) for other solid tumours. For childhood use of appliances, there was some suggestion of an increased risk associated with the use of an electric blanket. The odds ratios were 2.2 (95% CI, 0.7–6.4) for leukaemia, 1.6 (95% CI, 0.4–7.1) for tumours of the central nervous system and 2.4 (95% CI, 1.0–6.1) for other solid tumours. There was also the suggestion of an effect for electric heating, but only in the room occupied during the day (odds ratio, 1.8; 95% CI, 0.9–3.5), not in the child's bedroom (odds ratio, 1.0; 95% CI, 0.5–2.3).

2.2.3 *Parental exposure to ELF electric and magnetic fields*

(*a*) *Cohort study*

Feychting *et al*. (2000) conducted a cohort study on occupational exposure of parents to magnetic fields and cancer in offspring. Children born in Sweden in 1976, 1977, 1981 and 1982 were followed until 1993, and those who developed cancer before the age of 15 years were identified. A total of 522 children with cancer including 161 with leukaemias and 162 with cancer of the central nervous system were identified. The occupations of their mothers and fathers were taken from data recorded in the 1975 and

1980 censuses. The percentages of parents without a recorded job were 27.1% for mothers and 5.4% for fathers. The likelihood of occupational exposure to electric and magnetic fields was quantified through use of a job–exposure matrix. For children whose mothers had been exposed to magnetic fields ≥ 0.19 μT (third quartile) or ≥ 0.26 μT (90th percentile), the relative risks for all types of tumour were close to unity (relative risk, 1.1 (95% CI, 0.7–1.4) and relative risk, 1.1 (95% CI, 0.7–1.7), respectively). For children whose fathers had been exposed to magnetic fields ≥ 0.3 μT, the risk for leukaemia was elevated (relative risk, 2.0; 95% CI, 1.1–3.5) and the risk for cancers of the central nervous system was less than unity (relative risk, 0.5; 95% CI, 0.3–1.0).

(*b*) *Case–control studies*

In a case–control study of 157 children, less than 15 years of age, who had died of neuroblastoma during 1964–78 in Texas, USA, Spitz and Johnson (1985) reported an elevated risk for neuroblastoma (odds ratio, 2.1; 95% CI, 1.1–4.4) among the children of electrical workers. Data on parental occupation at birth of the child were abstracted from the birth certificate, and exposure was inferred from occupational title.

A subsequent hospital-based study on the incidence of neuroblastoma in Ohio, USA of 101 incident cases of neuroblastoma in children < 15 years old born during 1942–67 and 404 controls (Wilkins & Hundley, 1990) made use of information on paternal occupation from birth certificates to infer exposure, but found no association between employment of the father in an electrical occupation and risk of neuroblastoma in the offspring.

Bunin *et al*. (1990) conducted a small case–control study of neuroblastoma in 104 children diagnosed from 1970–79 at two hospital-based tumour registries in North-east USA. One hundred and four controls were selected by random-digit dialling. Data on parental occupation were obtained by telephone interview and exposure to electric and magnetic fields was classified using the same scheme as that used by Spitz and Johnson (1985). No association was seen between neuroblastoma in offspring, and exposure of fathers employed as electricians, insulation workers or power utility workers during the preconception period (odds ratio, 0.3; 95% CI, 0.1–1.2) or mother's exposure during pregnancy (same occupational groups as for fathers) (0.3; 95% CI, 0.1–1.3).

Nasca *et al.* (1988) conducted a case–control study of children with cancer and parental occupation. Three hundred and thirty-eight children (aged 0–14 years) with a primary tumour of the central nervous system diagnosed between 1968 and 1977 in 53 New York counties were included. Six hundred and seventy-six controls matched by age and geographical location were also selected. Parents were interviewed by telephone to obtain job information. Exposure was classified according to occupational title. No association was seen between cancer of the central nervous system in offspring and parental exposure to electric and magnetic fields before the birth of the child (odds ratio, 1.6; 95% CI, 0.83–3.1).

Wilkins and Koutras (1988) in Ohio, USA, conducted a case–control study of mortality from brain cancer during 1959–78. The study population included 491 offspring (< 20 years of age) of men whose job title suggested occupational exposure to electric and magnetic fields. An elevated risk of brain cancer was seen in the children of men involved in electrical assembly, installation and repairing occupations (odds ratio, 2.7; 95% CI, 1.2–6.1).

Johnson and Spitz (1989) conducted a mortality case–control study of all children under the age of 15 years who had died in Texas, USA from 1964–80 of intracranial and spinal cord tumours (499 cases, 998 controls). Data on parental occupation collected at birth of the children were used to infer exposure. For all occupational categories thought to involve potential exposure of parents to ELF electric and magnetic fields, the risk was marginally elevated (odds ratio, 1.6; 95% CI, 0.96–2.8) in the offspring.

Parental occupation as a risk factor for astrocytoma in children aged 0–14 was examined by Kuijten *et al*. (1992). The patients were identified through tumour registries in eight hospitals in Pennsylvania, New Jersey and Delaware (USA) and included all cases diagnosed from 1980–86. Controls were selected by random-digit dialling and were pair-matched to cases by age, race and telephone exchange. The mothers and fathers of the 158 case–control pairs were interviewed by telephone, and exposure to electric and magnetic fields was inferred from job title. In general no associations with childhood astrocytoma were seen; however, in a sub-analysis, men reported as being 'electrical repairing workers' during the preconception period had a significantly elevated risk of fathering a child who later developed astrocytoma (odds ratio, 8.0; 95% CI, 1.1–356).

Wilkins and Wellage (1996) identified 94 patients aged 20 years or less with tumours of the central nervous system who were diagnosed during the years 1975–82 through the Columbus Children's Hospital Tumor Registry (USA). Random-digit dialling was used to select 166 controls from the 48-county referral area of the registry. For fathers who had occupations presumed to have resulted in exposure to electric and magnetic fields during the period before conception, no elevated risk of cancer of the central nervous system was noted in their offspring. However, exposure of the father working in welding-related jobs during preconception was associated with an elevated risk (odds ratio, 3.8; 95% CI, 0.95–16).

2.3 Cancer in adults

2.3.1 *Residential exposure to ELF electric and magnetic fields*

In addition to the many methodological considerations discussed in other sections, including the lack of studies that have included a comprehensive assessment of exposure, residential studies of adults present unique difficulties. These problems are:

— the contribution of occupational exposure — not considered in most studies;
— the lack of assessment of other sources of exposure likely to be important for adults who spend only a fraction of their time at home;

— the long latency period for most adult malignancies, often necessitating assessment (owing to residential mobility) in several residences;
— the need to use proxy response for deceased cases; and
— low participation rates.

The assessment of exposure in most of the following studies was based either on proximity to electrical installations or on simple questions regarding appliance use. Few studies included spot measurements in several locations. Even long-term residential measurements are unlikely to capture the strength or variability of daily exposure for working adults. In a 1000-person study, Zaffanella and Kalton (1998) found that occupational exposure was often significantly higher and more variable than other sources of exposure; the highest mean and median exposure occurs at work, followed by exposure at home and during travel. Since most people spend much of their time at home, ignoring exposure either at home or at work is likely to lead to a large misclassification. In a small study of the use of household appliances, Mezei *et al*. (2001) found that a large proportion of total exposure for most adults is accumulated at home. Similarly, the 1000-person study found exposure at home to be moderately predictive of 24-h average exposure or of time spent in magnetic fields above 0.4 μT, but completely uncorrelated with maximum fields or with field changes.

The long latency of cancers in adults and the unknown biological mechanism necessitate estimation of exposure over long time periods, an exceptionally difficult task owing to the mobility and behavioural changes likely to occur with time. The situation is even more difficult for rapidly fatal diseases such as brain cancer about which information is generally obtained from numerous proxies.

Following the publication of the study by Wertheimer and Leeper (1979) suggesting an association between residential exposure to ELF magnetic fields and cancer in children (see p. 105), many studies have investigated the possible carcinogenic effects of electric and magnetic fields. Most of the epidemiological studies have focused on cancer in children (see section 2.2). Studies of adults have looked primarily at occupational exposure, but some have investigated residential settings. As shown in Table 24, which lists studies of residential adult cancer by exposure category, several studies have investigated links between the use of electric blankets and breast cancer. Many studies have examined proximity to power lines and cancer, focusing particularly on leukaemia and brain cancer, but studies in which a sophisticated assessment of exposure has been made are few.

The first study on residential exposure to ELF magnetic fields and adult cancer was conducted by Wertheimer and Leeper (1982) in the USA. [The Working Group noted that this was a hypothesis-generating paper, but its usefulness for hypothesis testing was compromised because of unblinded exposure assessment, potential overmatching for the Denver cases and the unusual and complex method for selection of cases and controls.]

Table 24. Residential studies of adult cancer by exposure category

Outcome	Exposure					
	Electric blanket	Other appliances	Proximity	Calculated fields	Spot measurements	Combined occupational and residential
Leukaemia						
Wertheimer & Leeper (1987)	–	–	4	–	–	–
McDowall (1986)	–	–	4	–	–	–
Coleman *et al*. (1989)	–	–	4	–	–	–
Youngson *et al*. (1991)	–	–	4	4	–	–
Schreiber *et al*. (1993)	–	–	4	–	–	–
Severson *et al*. (1988)	4	–	4	–	4	–
Feychting & Ahlbom (1994)	–	–	4	4	4	–
Feychting *et al*. (1997)	–	–	–	–	–	4
Verkasalo *et al*. (1996)	–	–	–	4	–	–
Li *et al*. (1997)	–	–	4	4	–	–
Preston-Martin *et al*. (1988)	4	–	–	–	–	–
Lovely *et al*. (1994)	–	4	–	–	–	–
Sussman & Kheifets (1996)	–	4	–	–	–	–
Brain						
Wertheimer & Leeper (1982, 1987)	–	–	4	–	–	–
Schreiber *et al*. (1993)	–	–	4	–	–	–
Feychting & Ahlbom (1994)	–	–	4	4	–	–
Feychting *et al*. (1997)	–	–	–	–	–	4
Verkasalo *et al*. (1996)	–	–	–	4	–	–
Li *et al*. (1997)	–	–	4	4	–	–
Wrensch *et al*. (1999)	–	–	4	–	4	–
Ryan *et al*. (1992)	4	4	–	–	–	4
Mutnick & Muscat (1997)	4	4	–	–	–	–

Table 24 (contd)

Outcome	Exposure					
	Electric blanket	Other appliances	Proximity	Calculated fields	Spot measurements	Combined occupational and residential
Breast						
Wertheimer & Leeper (1982; 1987)	–	–	4	–	–	–
McDowall (1986)	–	–	4	–	–	–
Schreiber *et al* (1993)	–	–	4	–	–	–
Verkasalo *et al* (1996)	–	–	–	4	–	–
Li *et al*. (1997)	–	–	4	4	–	–
Coogan & Aschengrau (1998)	4	4	4	–	–	4
Feychting *et al*. (1998)	–	–	–	4	–	–
Forssén *et al*. (2000)	–	–	–	–	–	4
Vena *et al*. (1991, 1994, 1995)	4	–	–	–	–	–
Gammon *et al*. (1998)	4	–	–	–	–	–
Laden *et al*. (2000)	4	–	–	–	–	–
Zheng *et al*. (2000)	4	4	–	–	–	–
Other cancers						
Wertheimer & Leeper (1982, 1987)	–	–	4	–	–	–
Verkasalo *et al.* (1996)	–	–	–	4	–	–
Zhu *et al*. (1999)	4	–	–	–	–	–

(*a*) *Leukaemia*

Early studies of leukaemia focused mostly on the potential association between proximity to power lines and cancer development. From 1971–83, McDowall (1986) followed a cohort of 7631 people in East Anglia, England, who lived within 50 m of a substation or other electrical installation, or within 30 m of overhead power lines at the time of the 1971 census. Coleman *et al*. (1989) conducted a case–control study of leukaemia and residential proximity to electric power facilities in four London boroughs. Seven hundred and seventy-one leukaemia cases diagnosed between 1965 and 1980 were identified from a population-based cancer registry. In a matched case–control study, Youngson *et al*. (1991) investigated adult haematological malignancies in relation to overhead power lines; the study included 3144 adults with leukaemia identified from regional cancer registries in north-west England and Yorkshire; controls were selected from hospital discharge listings. Schreiber *et al*. (1993) investigated mortality and residence near electric power facilities in a retrospective cohort study of 3549 people who lived for five consecutive years between 1956 and 1981 in an urban quarter of Maastricht, The Netherlands. Koifman *et al*. (1998) investigated cancer clusters near power lines in Brazil; small numbers and other methodological problems make the study uninformative for evaluation, and it is mentioned here only for completeness. [The Working Group noted that although some of these studies indicated a small, non-significant elevation of risk, they are based on small numbers, low potential exposures and very crude exposure assessment methods. The overall results are non-informative.]

Several studies of adult leukaemia deserve special mention, including Severson *et al*. (1988), Feychting and Ahlbom (1994), with a follow-up study by Feychting *et al*. (1997), and studies by Verkasalo (1996), Verkasalo *et al*. (1996) and Li *et al*. (1997) (see Table 25).

Severson *et al*. (1988) conducted a case–control study of 164 adults, both living and deceased, diagnosed with acute non-lymphocytic leukaemia in the USA. The patients studied were aged from 20–79 years, diagnosed between 1981 and 1984 and recorded in a population-based cancer registry in western Washington State. The response rate was 70%. For controls, the response rate was 65%. One hundred and fourteen patients (or the next-of-kin if the patient had died) and 133 controls completed detailed questionnaires on residential history and use of electrical appliances. Three different methods were used to assess exposure. (1) The wire-coding scheme of Wertheimer and Leeper (1979) was used to classify all homes in the study area in which a subject had lived in the previous 15 years. Residential magnetic fields were also estimated according to a method developed by Kaune *et al*. (1987) using wiring configuration maps of dwellings. (2) Single measurements of indoor and outdoor magnetic fields were made at the time of the interview in a subject's home if the subject had lived there continuously for one year or longer immediately preceding the reference date (controls) or the date of diagnosis (cases). Measurements were made in the kitchen, the subject's bedroom and the family room, under both low-power (all possible appliances

Table 25. Design and results of epidemiological studies of residential exposure to ELF magnetic fields and adult leukaemia

Reference, country	Study base and subject identification	Exposure metrics	Results	Comments
Severson *et al.* (1988) USA	**Case selection**: ANLL cases aged 20–79 years, resident in western Washington state, from cancer registry (1981–84). 114 cases included in analyses (91 AML) **Control selection**: controls from random-digit dialling, matched on geographical area and frequency matched on age and sex. 133 controls included in analyses	Wertheimer and Leeper wire-coding. Estimation of magnetic fields from maps and wire coding — method of Kaune *et al.* (1987). Single measurements of 60-Hz magnetic fields inside (kitchen, bedroom, family room in HPC and LPC) and outside house; 24-h measurements in sample of houses. Electric appliance use from questionnaire	Mean exposure, low-power configuration Ref.: ≤ 0.05 μT: OR (95% CI) Single measurements: 0.051–0.199 μT: 1.2 (0.52–2.6); ≥ 0.2 μT: 1.5 (0.48–4.7) Weighted mean: 0.051–0.199 μT: 1.2 (0.54–2.5); ≥ 0.2 μT: 1.0 (0.33–3.2)	Refusal rate for measurements much higher among controls than cases. Single measurements made in only 56% of houses as many subjects had moved recently
Feychting & Ahlbom (1994) Sweden	**Case selection**: All incident cancer cases from cancer registry (1960–85), from cohort of Swedish population aged ≥ 16 years, living on a property located within 300 m of any 220- or 400-kV power lines. 325 cases analysed (72 AML, 57 CML, 14 ALL and 132 CLL) **Control selection**: Two controls per case from same cohort. Matched on age, sex, parish and residence near same power line. 1091 controls in analysis	Distance to power lines from residence. In-home magnetic-field spot measurements under low- and high-power use conditions. Calculations were made of magnetic fields generated by power lines at the time of spot measurements (calculated contemporary fields) and for the year closest in time to diagnosis (calculated historical fields).	Calculated fields closest to time of diagnosis Ref.: ≤ 0.09 μT: No.: OR (95% CI) All leukaemia: 0.10–0.19 μT: 20: 0.9 (0.5–1.5); ≥ 0.2 μT: 26: 1.0 (0.7–1.7) AML: 0.10–0.19 μT: 5: 1.0 (0.4–2.5); ≥ 0.2 μT: 9: 1.7 (0.8–3.5)) CML: 0.10–0.19 μT: 2: 1.4 (0.5–3.3); ≥ 0.2 μT: 7: 1.7 (0.7–3.8) CLL: 0.10–0.19 μT: 8: 0.8 (0.4–1.7); ≥ 0.2 μT: 7: 0.7 (0.3–1.4)	Matched and unmatched analyses, adjusted or not for age and socioeconomic status were carried out. No information on other sources of residential exposure to electric and magnetic fields
Feychting *et al.* (1997) Sweden	Same as Feychting and Ahlbom (1994)	Same as above for residential. Occupational exposure from job–exposure matrix [developed from workday measurements made for another study] and information on occupation held in the year preceding the reference date	Subjects with both residential and occupational exposure Ref.: ≤ 0.1 μT res. and < 0.13 μT occ.: No.: OR (95% CI) All leukaemia: ≥ 0.2 μT for both: 9: 3.7 (1.5–9.4) AML: ≥ 0.2 μT for both: 3: 6.3 (1.5–26) CML: ≥ 0.2 μT for both: 3: 6.3 (1.5–27) CLL: ≥ 0.2 μT for both: 2: 2.1 (0.4–10)	Same as above. Job–exposure matrix. Relevance especially for females unclear

Table 25 (contd)

Reference, country	Study base and subject identification	Exposure metrics	Results				Comments
Verkasalo *et al.* (1996) Finland	**Cohort** consisting of 383 700 persons (189 300 men) aged 20 years or older who contributed 2.5 million person–years of follow-up between 1970 and 1989 **Case selection**: All primary leukaemia cases (1974–89) living within 500 m of overhead power lines. 203 cases identified	Cumulative exposure. Estimates based on residential history, distance to 110–400 kV power line in 500 m corridor and calculated average annual magnetic fields for each building presumed to be ≥ 0.01μT. Took into account current, typical locations of phase conductors and distance.	Cumulative exposure Ref.: general population		No.	SIR (95% CI)	Cohort study, SIRs. No information on other sources of residential exposure to electric and magnetic fields. No direct information from study subjects
			All leukaemia	< 0.20 μT	156	0.96 (0.82–1.1)	
				0.20–0.39 μT	23	1.1 (0.68–1.6)	
				0.40–0.99 μT	15	0.87 (0.49–1.4)	
				1.00–1.99 μT	5	0.81 (0.26–1.9)	
				≥ 2.0 μT	4	0.71 (0.19–1.8)	
Verkasalo (1996) Finland	**Case selection**: Same as Verkasalo *et al.* (1996): 196 leukaemia cases included (60 AML, 12 ALL, 30 CML, 73 CLL and 21 other or unknown subtype) **Control selection**: 10 controls per case from cohort. Matched on sex and age at diagnosis and alive in the year of diagnosis of the case	Cumulative exposure: total and within 0–4, 5–9 and ≥ 10 years of diagnosis. Annual average magnetic fields 1–20 years prior to diagnosis. Highest annual average magnetic field ever and in time windows before diagnosis. Age at first exposure to annual average magnetic field greater than a specific level. Duration and time since exposure to annual averages above that level	Cumulative exposure Ref.: < 0.2 μT–years		No.	OR (95% CI)	
			All leukaemia	≥ 2.0 μT–years	4	0.77 (0.28–2.2)	
			ALL	≥ 2.0 μT–years	none		
			AML	≥ 2.0 μT–years	none		
			CML	≥ 2.0 μT–years	none		
			CLL	≥ 2.0 μT–years	3	1.7 (0.48–5.8)	
Li *et al.* (1997)	**Case selection**: Pathologically confirmed incident cases of leukaemia from northern Taiwan from cancer registry (1987–92). 870 cases included in analyses **Control selection**: One control per case from cancer registry excluding cancers of the brain and breast, haematopoietic and reticulo-endothelial system, skin, ovary, fallopian tube and broad ligament. Matched on date of birth, sex and date of diagnosis. 889 controls included in analyses	Distance from lines. Average and maximum magnetic fields assessed using distance from the lines, distance between wires, height of wires above the ground, annual and maximum loads along the lines from 1987–92, current phase and geographical resistivity of earth	Calculated exposure in year of diagnosis Ref.: < 0.1 μT		No.	OR (95% CI)	Limited information on confounders because of restrictions on interview
			All leukaemia	0.1–0.2 μT	47	1.3 (0.8–1.9)	
				> 0.2 μT	97	1.4 (1.0–1.9)	
			ALL	0.1–0.2 μT	8	1.5 (0.7–3.2)	
				> 0.2 μT	17	1.7 (1.0–3.1)	
			AML	0.1–0.2 μT	28	1.5 (0.9–2.5)	
				> 0.2 μT	41	1.1 (0.7–1.7)	
			CML	0.1–0.2 μT	2	0.3 (0.1–1.2)	
				> 0.2 μT	22	1.5 (0.9–2.6)	
			CLL	0.1–0.2 μT	4	2.8 (0.9–9.3)	
				> 0.2 μT	3	0.6 (0.1–2.6)	

ANNL, acute non-lymphocytic leukaemia; AML, acute myeloid leukaemia; OR, odds ratio; CI, confidence interval; CML, chronic myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; SIR, standardized incidence ratio; HPC, high-power configuration; LPC, low-power configuration; res., residential; occ., occupational; Ref.:, reference group with exposure level indicated

turned off that could be (without overly disrupting the household) and high-power conditions (all such appliances switched on). (3) In a limited sample of dwellings, 24-h measurements were made. [However, neither details of the 24-h measurements nor the relevant results were given.] Cases tended to be of lower socioeconomic status than controls and were more likely to smoke or to have smoked in the past; these factors were adjusted for in subsequent analyses. No association was found between acute non-lymphocytic leukaemia and wire codes, either in the dwelling occupied for the longest period in the 3–10 years before the reference date or in the dwelling occupied closest to the reference date. There was also no association with TWA exposure to residential magnetic fields. For single measurements, available for only 56% of homes since many subjects had moved house after the reference date, a non-significant increase in odds ratio was found for mean exposures of ≥ 0.2 μT in both low-power (odds ratio, 1.5; 95% CI, 0.48–4.7) and high-power conditions (odds ratio, 1.6; 95% CI, 0.49–5.0). When weighted mean exposure was considered, the increase was no longer apparent in low-power conditions and was reduced in high-power conditions (odds ratio, 1.3; 95% CI, 0.35–4.5). [The Working Group noted that the participation rates in this study were low.]

Feychting and Ahlbom (1992a,b; 1994) conducted a nested case–control study of leukaemia and cancer of the central nervous system in a Swedish population who had lived for at least one year within 300 m of overhead 220- and 400-kV power lines between 1960 and 1985. The adult study population included 400 000 people ≥ 16 years of age, identified from the Population Registry, who lived on properties designated using maps from the Central Board for Real Estate Data, as being located within the power-line corridor. From this cohort, leukaemia cases were identified by record linkage with the Swedish Cancer Registry. Two controls for each case were selected at random from members of the cohort who had lived in the power-line corridor at least one year before the reference date (year of diagnosis of the case) and lived near the same power line as the corresponding case. Cases and controls were matched on age (within five years), sex, parish of residence and year of diagnosis. A total of 325 cases of leukaemia and 1091 controls were included in the analysis. Seventy-two of the cases had acute myeloid leukaemia, 57 chronic myeloid leukaemia, 14 acute lymphoblastic leukaemia, 132 chronic lymphocytic leukaemia and 50 had other types of leukaemia. In addition to spot measurements and distance from power lines, exposure metrics included estimated magnetic fields within residences as a function of their proximity to the lines. These fields were calculated from an engineering model that took into account past exposure (dating back to 1947, over more than three decades), physical dimensions of lines and their distance from a dwelling. The model served as the primary exposure index. Magnetic field strengths were estimated from calculations for the year of diagnosis, or the year closest to diagnosis if the subject had moved, as well as for one, five and 10 years before diagnosis. Cumulative exposure was also calculated by summing yearly averages for exposure to magnetic fields assigned to each of the 15 years before diagnosis. The study included

information on age, sex, year of diagnosis, whether or not the subject resided in the county of Stockholm, type of housing and socioeconomic status. Some types of leukaemia were positively associated with fields calculated from the historical model and with proximity to the power line, but not with spot measurements. There was no association between the risk for all leukaemias and calculated exposure to magnetic fields closest to the time of diagnosis. For acute and chronic myeloid leukaemias, however, odds ratios were non-significantly increased for fields ≥ 0.2 μT compared with fields ≤ 0.09 μT. For acute myeloid leukaemia, the odds ratio, based on nine exposed cases, was 1.7 (95% CI, 0.8–3.5); for chronic myeloid leukaemia, the odds ratio, based on seven exposed cases, was 1.7 (95% CI, 0.7–3.8). For analyses based on calculated cumulative exposure during the 15 years preceding diagnosis, the odds ratios for all leukaemias were 1.0 (95% CI, 0.6–1.8) for cumulative exposures of 1.0–1.9 μT–years (16 cases), 1.5 (95% CI, 1.0–2.4) for ≥ 2.0 μT–years (29 cases) and 1.5 (95% CI, 0.9–2.6) for ≥ 3.0 μT–years (19 cases), in comparison with ≤ 0.99 μT–years. Odds ratios were increased for exposure ≥ 2.0 μT–years for acute myeloid leukaemia (odds ratio, 2.3; 95% CI, 1.0–4.6) (nine cases) and for exposure > 3.0 μT–years for chronic myeloid leukaemia (odds ratio, 2.7; 95% CI, 1.0–6.4) (6 cases). Adjustment for age and socioeconomic status had little effect on the results. Also, the results of matched analyses were similar to those of the unmatched analyses. For analyses based on spot measurements, odds ratios were close to unity for all categories of exposure and for all leukaemia subtypes, except for chronic myeloid leukaemia in the ≥ 0.2-μT category (odds ratio, 1.5; 95% CI, 0.7–3.2) (10 cases). [The Working Group noted that exposure assessment for leukaemia was complicated by the long time-period covered by the study, which necessitated estimation of field strengths going back 25 years or more.]

Feychting *et al*. (1997) conducted a follow-up study using the same study base together with information on occupation taken from censuses performed by Statistics Sweden every five years. For the occupation held in the year before the reference date, they assessed exposure based on a job–exposure matrix from a previous study (Floderus *et al*., 1993, 1996). In that study, workday measurements had been made for a large number of jobs held by a sample of the general male population; consequently, no information was available on the occupations of 43% of the women. Combined analysis of residential and occupational exposure showed that subjects who had only residential exposure in the highest category (compared with 'unexposed' subjects with residential exposure < 0.1 μT and occupational exposure < 0.13 μT) had the following odds ratios: for acute myeloid leukaemia, 1.3 (95% CI, 0.4–5.0) (3 cases), and for chronic myeloid leukaemia, 0.5 (95% CI, 0.1–3.9) (1 case). [The very small number of cases prevents any interpretation of these results.] The odds ratios for subjects who had both high occupational and high residential exposure were much higher: for acute myeloid leukaemia, the odds ratio was 6.3 (1.5–26) and for chronic myeloid leukaemia the odds ratio was 6.3 (95% CI, 1.5–27), based on three exposed cases of each subtype). [The Working Group noted that the limitations of the previous study also

apply to this one. The information on occupational exposure was difficult to interpret because of the limited applicability of the job–exposure matrix to this population.]

In a nationwide cohort study of 383 700 adults in Finland, Verkasalo *et al*. (1996) investigated cancer risk and exposure to magnetic fields in homes near high-voltage power lines. The cohort included all adults who had lived within 500 m of overhead power lines in homes with calculated magnetic field strengths of ≥ 0.01 μT at any time between 1970 and 1989. Through record linkage between nationwide data files (from the Finnish Cancer Registry, the Central Population Register, the 1970 Population Census, and the five Finnish power companies), information was obtained on cancer cases, residential history and residential exposure to magnetic fields. Follow-up took place from January 1974 until December 1989. Verkasalo (1996) presented a detailed case–control analysis of leukaemia. Of a total of 196 patients with leukaemia included in the study, 60 had acute myeloid leukaemia, 12 acute lymphoblastic leukaemia, 30 chronic myeloid leukaemia, 73 chronic lymphocytic leukaemia and 21 other, or unknown, subtypes. For each case, 10 controls were selected from the cohort and matched on sex, age at diagnosis of the case (within one year) and whether they were alive in the year of diagnosis. Several exposure measures were used. These included cumulative exposure and exposure 0–4, 5–9 and ≥ 10 years before diagnosis; annual average magnetic fields 1–20 years before diagnosis; highest annual average magnetic field 0–4, 5–9 and ≥10 years before diagnosis; age at first exposure to an annual average magnetic field greater than a specified strength; and duration of exposure and time since exposure to annual averages above that strength. No association was seen between the risk for all leukaemias or for specific subtypes and cumulative exposure or highest annual average exposure. Adjustment for type of housing or for occupational exposure (none versus possible or probable, based on expert judgement) did not affect the results. On the basis of three exposed cases, the study showed a significant increase in risk for chronic lymphocytic leukaemia with dichotomized cumulative exposure of ≥ 0.2 μT–years and ≥ 0.4 μT–years for ≥ 10 years before diagnosis (odds ratios, 2.8 (95% CI, 1.1–7.4) (9 cases) and 4.6 (95% CI, 1.4–15) (6 cases), respectively) and for duration of exposure to fields of ≥ 0.1 μT for ≥ 12 years (odds ratio, 4.8; 95% CI, 1.5–15) (3 cases). No association was observed for other types of leukaemia. [The Working Group noted that no measurements were made to validate the calculated fields in this study, and that the lack of information on other sources of residential exposure to electric and magnetic fields might have resulted in substantial exposure misclassification.]

Li *et al*. (1997) conducted a case–control study of leukaemia and other cancers in adults living in northern Taiwan. Cases and controls were ≥ 15 years of age and diagnosed with leukaemia between 1987 and 1992 and were selected from the National Cancer Registry of Taiwan. Controls were adults with cancers other than those potentially related to exposure to magnetic fields. Each case was matched with one control based on age, sex and date of diagnosis. Maps showing the location of each dwelling were available for only 69% of the study area; the lack of such maps was the primary

reason for exclusion from the study. Power-company maps showed that 121 high-voltage power lines (69–345 kV) were operating in the study area between 1987 and 1992. The distance between each dwelling occupied by a study subject at the time of diagnosis and the nearest power line was measured from the maps with a precision of 10 m. Residential exposure was calculated from data supplied by the Taiwan Power Company that included distance between wires, height of wires above the ground, annual average and maximum loads and current phase. Calculated magnetic fields were validated by indoor measurements made with an EMDEX meter under low-power conditions (household power turned off) for 30–40 min in 407 residences. Questionnaire data on age, weight, height, educational level, smoking habits and previous exposure to X-rays were available for approximately one-third of study subjects. Information was obtained on potential confounding factors including urbanization (which took into consideration local population density), age, mobility, economic activity and family income, educational level and sanitation facilities. Of 1135 initial cases 870 incident cases of leukaemia were included in the analysis. [Not enough detail was provided to estimate the participation rate for controls.] The numbers of controls for cases of leukaemia living within 100 m and 50 m from the power lines were 10.9% and 5.4%, respectively. Of the controls, 9.9% had a calculated exposure of ≥ 0.2 μT and 5.6% had a calculated exposure of ≥ 0.5 μT. When the results were grouped into three exposure categories (< 0.1 μT, 0.1–0.2 μT and > 0.2 μT), the agreement (κ) between arithmetic means for measured and calculated fields was 0.64 (95% CI, 0.50–0.78). Compared with subjects living ≥ 100 m from the power lines, subjects who lived within 50 m of the lines had an odds ratio for leukaemia of 2.0 (95% CI, 1.4–2.9). For subjects whose homes were 50–99 m from the lines, the odds ratio was 1.5 (95% CI, 1.1–2.3). For calculated magnetic fields, the odds ratios for leukaemia were moderately elevated in the middle and highest exposure categories in the year of diagnosis: odds ratio, 1.3 (95% CI, 0.8–1.9) for exposure to 0.1–0.2 μT and odds ratio, 1.4 (95% CI, 1.0–1.9) for > 0.2 μT, compared with < 0.1 μT. A test for trend with increased exposure to magnetic fields was statistically significant ($p = 0.04$). [The Working Group noted the use of other cancer cases as controls and the low participation rate. Information on the power distribution systems near the dwellings of the study subjects was apparently unavailable. The ± 10-m precision of distance could have had a significant impact on calculations for dwellings within 20 m of power lines, but would contribute less error for those further away. Because the study was based on the dwelling occupied at the time of diagnosis, cumulative estimates of exposure to magnetic fields could not be calculated. Although examination of potential confounders in a subset of control subjects indicated little confounding from education, smoking, exposure to X-rays and reproductive factors, the authors were unable to adequately adjust for these risk factors for leukaemia.]

— *Appliance use*

A case–control study of leukaemia and use of electric blankets in the USA conducted by Preston-Martin *et al.* (1988) included patients aged 20–69 years, identified through

the population-based Los Angeles County cancer registry, who had been diagnosed with histologically confirmed acute or chronic myeloid leukaemia between July 1979 and June 1985. Of 858 eligible cases, 485 who were still living were chosen, and permission to contact 415 of them was obtained from their physicians. [The Working Group noted that inclusion of only living patients might lead to bias, if exposure influences survival.] Completed questionnaires were available for 295 of the 415 patients, resulting in a participation rate of 61%. Each case was matched with one neighbourhood control on sex, race and birth year (within five years). [The authors did not give the response rate for controls, but stated that controls could not be found in three neighbourhoods.] In all, 293 matched pairs, including 156 cases of acute myeloid leukaemia and 137 of chronic myeloid leukaemia, participated in the study. Because questions on use of electric blankets were added after the study had begun, information on their use was available for only 224 matched pairs. The results indicated that use of electric blankets was not related to risk of leukaemia. For acute myeloid leukaemia, the odds ratio was 0.9 (95% CI, 0.5–1.6) and that for chronic myeloid leukaemia was 0.8 (95% CI, 0.4–1.6). Cases and controls did not differ with regard to average duration of use, year of first regular use, or number of years since last use. Adjustment for other significant risk factors did not change the results. [The Working Group noted that the study did not indicate whether blankets had been used only for pre-warming the bed or continuously throughout the night.]

The study by Severson *et al*. (1988), described above, used questionnaires to obtain information on ownership and use of 32 [Lovely *et al.*, 1994] electrical domestic appliances. The study showed no association between risk of leukaemia and use of electric blankets, water-bed heaters or heated mattress pads. [The Working Group noted that participation rates in this study were low and limited information was available on use of electric blankets.]

The data from the study by Severson *et al*. (1988) were reanalysed by Lovely *et al*. (1994) and Sussman & Kheifets (1996). The bias due to the use of proxy respondents was noted by Sussman & Kheifets (1996) in the positive findings for the use of an electric razor (> 7.5 minutes/day) (odds ratio, 2.4; 95% CI, 1.1–5.5) reported by Severson *et al.* (1988).

(*b*) *Brain cancer*

Few studies, summarized in Table 26, have investigated the potential association between adult brain cancer and residential exposure to ELF magnetic fields. [Although several studies of adult cancers have examined cancer of the brain or nervous system as a subtype, results have been unremarkable (Wertheimer & Leeper, 1982; Schreiber *et al.*, 1993)]. Studies by Feychting and Ahlbom (1992a,b, 1994), Feychting *et al*. (1997), Verkasalo *et al*. (1996) and Li *et al*. (1997), which are described in detail in section *(a)*, also analysed brain cancer risk.

The population-based, nested case–control study of Feychting and Ahlbom (1992a,b, 1994) investigated exposure to magnetic fields from high-voltage power lines

Table 26. Design and results of epidemiological studies of residential exposures to ELF magnetic fields and adult brain cancer

Reference, country	Study base and subject identification	Exposure metrics	Results				Comments
Feychting & Ahlbom (1994) Sweden	**Case selection**: All incident cancer cases from cancer registry (1960–85), from cohort of Swedish population aged ≥ 16 years, living on a property located within 300 m of any 220- or 400-kV power lines. 223 cases in analysis (66 astrocytoma I–II, 157 astrocytoma III–IV) **Control selection**: Two controls per case from same cohort. Matched on age, sex, parish and residence near same power line; 1091 controls in analysis	Distance to power lines from dwelling. In-home spot measurements of magnetic fields under low- and high-power use conditions. Calculations of the magnetic fields generated by the power lines at the time spot measurements were made (calculated contemporary fields), and for the year closest in time to diagnosis (calculated historical fields).	Calculated fields closest to time of diagnosis				Matched and unmatched analyses, adjusted or not for age and socioeconomic status were carried out. No information on other sources of residential exposure to electric and magnetic fields
				Ref.: ≤ 0.09 μT	No. of cases	OR (95% CI)	
			All CNS	0.10–0.19 μT	18	1.1 (0.7–2.0)	
				≥ 0.2 μT	12	0.7 (0.4–1.3)	
			Astrocytoma I–II	0.10–0.19 μT	3	0.6 (0.1–1.8)	
				≥ 0.2 μT	2	0.4 (0.1–1.3)	
			Astrocytoma III–IV	0.10–0.19 μT	15	1.4 (0.8–2.5)	
				≥ 0.2 μT	10	0.8 (0.4–1.7)	
Feychting *et al.* (1997) Sweden	Same as Feychting and Ahlbom (1994)	Same as above for residential. Occupational exposure from job–exposure matrix [developed from workday measurements made for another study] and information on occupation held in the year before the reference date	Subjects with both residential and occupational exposure				Same as above. Job–exposure matrix. Relevance especially for females unclear
			Ref.: ≤ 0.1 μT res. and < 0.13 μT occ.		No. of cases	RR (95% CI)	
			All CNS	≥ 0.2 μT for both	3	1.3 (0.3–4.8)	
			Astrocytoma I–II	≥ 0.2 μT for both	0		
			Astrocytoma III–IV	≥ 0.2 μT for both	3	2.2 (0.6–8.5)	
Verkasalo *et al.* (1996) Finland	**Cohort:** 383 700 persons (189 300 men) aged ≥ 20 who contributed 2.5 million person–years of follow-up between 1970 and 1989 **Case selection**: All primary brain cancer cases (1974–89) living within 500 m of overhead power lines; 301 cases identified	Cumulative exposure. Estimates based on residential history, distance to 110–400-kV power line in 500-m corridor and calculated average annual magnetic fields for each building presumed to be ≥ 0.01μT. Takes into account current, typical locations of phase conductors and distance.	Cumulative exposure				Cohort study, SIRs. No information on other sources of residential exposure to electric and magnetic fields. No direct information from study subjects. ICD-7 code 193
			Ref.: general population		No. of cases	SIR (95% CI)	
			Nervous system	< 0.20 μT	238	0.94 (0.82–1.1)	
				0.20–0.39 μT	35	1.1 (0.77–1.5)	
				0.40–0.99 μT	16	0.64 (0.37–1.0)	
				1.00–1.99 μT	5	0.55 (0.18–1.3)	
				≥ 2.0 μT	7	0.92 (0.37–1.9)	

Table 26 (contd)

Reference, country	Study base and subject identification	Exposure metrics	Results				Comments
Li *et al.* (1997)	**Case selection**: Pathologically confirmed incident cases of brain cancer from northern Taiwan from cancer registry (1987–92). 577 cases included in analyses. **Control selection**: One control per case from cancer registry excluding cancers of brain and breast, of the haematopoietic and reticulo-endothelial system, skin, ovary, fallopian tube, and broad ligament. Matched on date of birth, sex and date of diagnosis. 552 controls included in analyses	Distance from lines. Average and maximum magnetic fields assessed using distance from the lines, distance between wires, height of wires above the ground, annual and maximum loads along the lines from 1987–92, current phase and geographical resistivity of the earth	Calculated exposure in year of diagnosis				Limited information on confounders because of restrictions on interview
			Ref.: < 0.1 μT		No. of cases	OR (95% CI)	
			All brain tumours	0.1–0.2 μT	23	0.9 (0.5–1.7)	
				> 0.2 μT	71	1.1 (0.8–1.6)	
			Astrocytoma	0.1–0.2 μT	4	0.6 (0.2–1.8)	
				> 0.2 μT	16	0.8 (0.5–1.5)	
			Glioblastoma	0.1–0.2 μT	8	1.3 (0.5–2.9)	
				> 0.2 μT	19	1.1 (0.6–2.0)	
			Oligodendro-glioma	0.1–0.2 μT	3	2.8 (0.8–10.4)	
				> 0.2 μT	2	0.6 (0.1–2.5)	
Wrensch *et al.* (1999)	**Case selection** Study of adult glioma in the San Francisco Bay Area. 492 newly diagnosed cases between 1991 and 1994 identified through the Northern California Cancer Center. **Control selection** 462 controls identified through random-digit dialling. Controls were matched to cases on age, sex and ethnicity.	For current dwellings and for all other California dwellings occupied during the 7 years before the study, exposure was assessed through spot measurements, wire codes and characterization of electrical facilities located within 150 feet [46 m] of the dwelling	Calculated exposure in year of diagnosis				Information was obtained from a proxy for 47% of the cases. 85% of the gliomas were glioblastomas multiforme or astrocytomas.
			Ref.: < 0.1 μT		No. of cases	OR (95% CI)	
			Glioma	0.1–0.2 μT	62	0.97 (0.7–1.4)	
				0.2–0.3 μT	15	0.6 (0.3–1.1)	
				> 0.3 μT	20	1.7 (0.8–3.6)	

CNS, central nervous system; SIR, standardized incidence ratio; OR, odds ratio; ref., reference exposure; ICD, International Classification of Disease; res., residential; occ., occupational; Ref.:, reference group with exposure level indicated

and risk for tumours of the central nervous system. The study examined 223 patients with brain tumours, including 66 with glioma (astrocytoma I and II) and 157 with glioblastoma (astrocytoma III and IV). There was no evidence of any association, whether exposure was assessed by spot measurements or by calculation of magnetic fields from power lines.

Feychting *et al*. (1997) combined residential and occupational exposure by incorporating estimates of occupational exposure to magnetic fields into their earlier residential study (Feychting & Ahlbom, 1994). They estimated residential exposure from calculated magnetic fields and occupational exposure from census information linked to a job–exposure matrix based on magnetic field measurements. Adults exposed to stronger magnetic fields both at home and at work showed no association between occupational or residential exposure and tumours of central nervous system. [The study also found no association for calculated residential exposure after exclusion of subjects who were not exposed at home but were exposed to field strengths ≥ 0.2 μT at work.] There was also no association when analyses were restricted to people who had only residential exposure (≥ 0.2 μT) (odds ratio, 0.7; 95% Cl, 0.3–1.7; 7 exposed cases). [The Working Group comments on the limitations of this study are given in section (*a*). However, this study is important in that it attempted to incorporate both residential and occupational exposure.]

Verkasalo *et al*. (1996), in their study of a cohort of 383 700 persons, investigated 301 cases of tumour of the nervous system and found no difference in incidence between members of the cohort and the general Finnish population. They also observed no association with calculated cumulative exposure to magnetic fields. The SIRs with respect to the general population were 0.94 (95% CI, 0.8–1.1; 238 cases) for exposures < 0.2 μT, 1.1 (95% CI, 0.77–1.5; 35 cases) for 0.2–0.39 μT, 0.64 (95% CI, 0.37–1.0; 16 cases) for 0.4–0.99 μT, 0.55 (95% CI, 0.18–1.3; 5 cases) for 1.00–1.99 μT and 0.92 (95% CI, 0.37–1.9; 7 cases) for ≥ 2.0 μT. Although the authors analysed gliomas and meningiomas separately, they reported only that the results were consistent with those for tumours of the nervous system as a whole. [See comments on the limitations of this study in section *(a)*.]

The case–control study of Li *et al*. (1997) described in section (*a*) examined 705 histologically confirmed incident cases of brain tumour (ICD[1]-9 191) in 45 districts of northern Taiwan. After exclusion of subjects residing in 14 of the districts because maps were not available, 577 cases and 552 controls remained. The study found no association between brain tumours and calculated exposure to magnetic fields in the year of diagnosis. Compared with the < 0.1 μT exposure category, the odds ratio for exposure of 0.1–0.2 μT was 0.9 (95% CI, 0.5–1.7; 23 cases) and that for exposure > 0.2 μT was 1.1 (95% CI, 0. 8–1.6; 71 cases). In analyses by tumour subtype, the odds ratios ranged from 0.6–2.8. [See comments on the limitations of this study in section *(a)*.]

[1] International Classification of Diseases

A large study by Wrensch *et al*. (1999) investigated adult glioma and residential exposure to electric and magnetic fields in six San Francisco Bay Area counties. The eligible cases were all adults newly diagnosed with glioma between 1 August 1991 and 31 March 1994. The study included 492 cases (82% of 603 eligible) and 462 controls (63% of 732 eligible), identified through random-digit dialling. Controls were frequency-matched to cases on age, sex and ethnicity. The average age of subjects was 54 years; 83% were white and 57% were male. Interviews were conducted in person in the homes of consenting patients (or their proxies) and controls. The interviewers asked about all dwellings occupied by subjects for three months or more for 15 years before either diagnosis (for cases) or interview (for controls). They also enquired about the subject's family and personal medical history, occupation, diet, smoking habits and alcohol use. The original diagnosis for 85% of cases was glioblastoma multiforme or astrocytoma; the remainder had other types of glioma. Proxy interviews were conducted for 233 cases (47%): 50% of the proxies were spouses of the cases, 30% were their children, 9% were siblings, 4% were parents and 7% had other relationships to the cases. Questionnaires covered a 15-year exposure period, for which 954 subjects reported 2995 dwellings. Usable addresses for all dwellings occupied during the seven years prior to diagnosis or study entry were obtained for 81.7% of cases and 84.2% of controls giving 1723 dwellings in California. Exposure assessment for electric and magnetic fields was completed for 81% of case and 86% of control dwellings. Exposure was assessed using indoor and outdoor spot measurements; characterization of power lines, transformers and substations located within 150 feet [46 m] of the dwelling, and Wertheimer–Leeper and Kaune–Savitz wire codes. To determine wire-codes, trained field workers made standardized drawings of all power lines within 150 feet [46 m] of each dwelling. Within this distance, they categorized up to three lines as to highest current type. For houses, they determined the shortest distance from the lines to the house. For apartments, they measured the distance from the nearest power line to the nearest boundary wall of each unit. For index dwellings, defined as the current dwelling for controls or the dwelling at time of diagnosis for cases, spot measurements were made in the centre of the kitchen, family room and bedroom, at the front door, and at the four outdoor corners of the dwelling. In addition, each subject selected a room in which a meter ran during the in-home interview. Spot measurements were also made with EMDEX meters under up to three power lines within 150 feet [46 m] of both current and previous dwellings and at the front doors of previous dwellings. The odds ratio for the longest-occupied dwellings with high compared with low Kaune–Savitz wire codes was 0.9 (95% CI, 0.7–1.3). For spot measurements at the front door (longest-occupied dwelling), the odds ratios for exposures of 0.1–0.2 μT, 0.2–0.3 μT and > 0.3 μT compared with ≤ 0.1 μT were 1.0 (95% CI, 0.7–1.4), 0.6 (95% CI, 0.3–1.1) and 1.7 (95% CI, 0.8–3.6), respectively. Adjusting for age, sex, ethnicity and whether subjects owned their homes did not meaningfully change the results, nor did restricting analyses to the subjects' highest wire-coded or index dwellings, or to single-family homes. The authors pointed out that there was no difference between cases and

controls in the cumulative distribution of average front door, average indoor or maximum EMDEX readings. [The Working Group noted that the use of random-digit dialling for control selection may have resulted in a control group that was not fully representative of the base population from which the cases arose. Information was obtained from proxies for 47% of the cases.]

— *Appliance use*

Two studies investigated whether the risk for adult brain tumours might be associated with the use of electric blankets and other domestic appliances. In an Australian brain tumour study, Ryan *et al*. (1992) used a questionnaire to obtain information on 110 incident cases of glioma and 60 of meningioma diagnosed in 1987–90, and 417 controls. The questionnaire was designed to examine the risk factors for brain tumour associated with the use of electric blankets and electrically heated water beds. Proxy or assisted interviews were necessary for 41% of cases and 7% of controls. [The data for direct and proxy interviews were not presented separately, but the authors stated that they found no important differences.] A non-significant excess risk (odds ratio, 1.5; 95% CI, 0.83–2.6) associated with the use of electric blankets was reported for glioma, but not for meningioma (odds ratio, 0.86; 95% CI, 0.39–1.9). The opposite was true for electrically-heated water beds (odds ratio, 0.67 (95% CI, 0.18–2.5) and 1.3 (95% CI, 0.25–6.4), for glioma and meningioma, respectively). [The power of the study for this exposure is not known, as the prevalence of use of electrically heated bedding was not given.] A second report (Mutnick & Muscat, 1997) presented a preliminary summary of the data collected so far in a hospital-based, case–control study of 328 patients with primary brain cancers (284 controls) in the USA (New York University Medical Center, Memorial Sloan-Kettering Cancer Center and Rhode Island Hospital). The authors reported no risk associated with regular use of a number of electrical appliances, including computers, electric blankets, hair dryers, razors, and bedside dial clocks. [The Working Group noted that aspects of the methodology (e.g. the low participation rate, the need for proxies, etc.) render this study uninformative.]

(*c*) *Breast cancer* (see Table 27)

The studies by Wertheimer and Leeper (1982, 1987), McDowall (1986) (in women) and Schreiber *et al*. (1993) (in women) also reported on breast cancer. The Working Group found the results of these studies uninformative.

Verkasalo *et al*. (1996) assessed the risk of breast cancer in their nationwide cohort study of Finnish adults described in the section on Leukaemia on p. 152. Of 194 400 women in the cohort, 1229 had been diagnosed with breast cancer. The SIRs were 1.1 (95% CI, 0.98–1.1; 945 cases) for exposure to fields of < 0.20 μT, 1.1 (95% CI, 0.88–1.3; 130 cases) for 0.20–0.39 μT, 0.89 (95% CI, 0.71–1.1; 87 cases) for 0.40–0.99 μT, 1.2 (95% CI, 0.89–1.6; 44 cases) for 1.00–1.99 μT and 0.75 (95% CI, 0.48–1.1; 23 cases) for ≥ 2.0 μT. [For comments on the limitations of this study, see section *(a)*.]

Table 27. Design and results of epidemiological studies of residential exposures to magnetic fields and breast cancer

Reference, country	Study base and subject identification	Exposure metrics	Results	Comments
Verkasalo *et al*. (1996) Finland (women)	**Cohort**: 383 700 persons (194 400 women) aged 20 or older who contributed 2.5 million person–years of follow-up between the years 1970 and 1989 **Case selection**: All primary breast cancer cases (1974–89) living within 500 m of overhead power lines: 1229 cases identified	Cumulative exposure. Estimates based on residential history, distance to 110–400-kV power line in 500-m corridor and calculated average annual magnetic fields for each building presumed to be ≥ 0.01μT. Took into account current, typical locations of phase conductors and distance.	Cumulative exposure Ref.: general population Breast cancer: > 0.20 μT, 945, 1.1 (0.98–1.1); 0.20–0.39 μT, 130, 1.1 (0.88–1.3); 0.40–0.99 μT, 87, 0.89 (0.7–1.1); 1.00–1.99 μT, 44, 1.2 (0.89–1.6); ≥ 2.0 μT, 23, 0.75 (0.48–1.1)	Cohort study, SIRs. No information on other sources of residential exposure to electric and magnetic fields. No direct information from study subjects.
Li *et al*. (1997) Taiwan (women)	**Case selection**: Pathologically confirmed incident cases of breast cancer from northern Taiwan from cancer registry (1990–92). 1980 cases included in analyses **Control selection**: One control per case from cancer registry excluding cancers of the brain and breast, of the haematopoietic and reticulo-endothelial system, skin, ovary, fallopian tube and broad ligament. Matched on date of birth, sex and date of diagnosis: 1880 controls included in analyses	Distance from lines. Average and maximum magnetic fields assessed using distance from the lines, distance between wires, height of wires above the ground, annual and maximum loads along the lines from 1987–92, current phase and geographical resistivity of earth	Calculated exposure in year of diagnosis Ref.: < 0.1 μT All breast cancers: 0.1–0.2 μT, 107, 1.1 (0.8–1.5); > 0.2 μT, 224, 1.1 (0.9–1.3) Group I: 0.1–0.2 μT, 89, 1.0 (0.8–1.4); > 0.2 μT, 193, 1.0 (0.8–1.2) Group II: 0.1–0.2 μT, 0, –; > 0.2 μT, 7, 0.9 (0.6–1.3) Group III: 0.1–0.2 μT, 3, 1.3 (0.4–4.2); > 0.2 μT, 8, 1.5 (0.7–3.2)	Limited information on confounders because of restrictions on interview
Coogan & Aschengrau (1998) USA (women)	**Case selection**: Cases diagnosed between 1983 and 1986 in Cape Cod. Of 334 cases reported, 259 were included in the analysis. **Control selection**: Controls identified from three sources — random-digit dialling, lists of Medicare beneficiaries and death certificates. The 738 controls were matched on age, vital status (and if deceased, on year of death).	Use of electrically heated bedding, occupational history since age 18 years and residential history from 1943. Residential exposure was determined from proximity (within 152 m) to power lines and substations for dwellings on Cape Cod. Occupations were assigned to one of three categories (high, medium and no exposure).	Proximity to power lines/substations Breast cancer: 1–5 years, 7, 1.3 (0.5–3.6); > 5 years, 4, 1.7 (0.4–6.3)	Adjusted OR. No measurement data are presented, no sources are cited. The grouping of occupations differs from that used by most other investigators.

Table 27 (contd)

Reference, country	Study base and subject identification	Exposure metrics	Results				Comments
Feychting *et al*. (1998a) Sweden (men and women)	**Case selection**: All incident cancer cases from cancer registry (1960–85), from cohort of Swedish population aged ≥ 16 years, living in single family homes, located within 300 m of any 220- or 400- kV power lines: 699 women, 9 men **Control selection**: One control per case from same cohort. Matched on age, sex, parish and residence near same power line: 699 controls	Distance to power lines from dwelling. Calculations of the magnetic fields generated by the power lines	Calculated fields closest to time at diagnosis				Highest OR, 7.4 (1.0–178) for ER+ and less than 50 years of age
				Ref.: ≤ 0.09 μT	No. of cases	OR (95% CI)	
			Women				
			All ages	0.10–0.19 μT	57	1.2 (0.8–1.8)	
				≥ 0.2 μT	54	1.0 (0.7–1.5)	
			< 50 years	0.10–0.19 μT	14	1.2 (0.6–2.8)	
				≥ 0.2 μT	15	1.8 (0.7–4.3)	
			≥ 50 years	0.10–0.19 μT	43	1.2 (0.7–1.9)	
				≥ 0.2 μT	39	0.9 (0.5–1.4)	
			Men	≥ 0.2 μT	2	2.1 (0.3–14)	
Forssén *et al*. (2000) Sweden (women)	Same as Feychting *et al*. (1998a), but expanded to include apartments; 1767 cases and 1766 controls	Same as above for residential. Occupational exposure from job–exposure matrix [developed from workday measurements made for another study] and information on occupation held in the year before the reference date	Subjects with both residential and occupational exposure				Number of cases with ER– is zero.
				Ref.: < 0.1 μT res. and < 0.12 μT occ.	No.	OR (95% CI)	
			All ages	≥ 0.1 μT res., ≥ 0.12 μT occ.	8	0.9 (0.3–2.7)	
			< 50 years		4	7.3 (0.7–78.3)	
			≥ 50 years	≥ 0.1 μT res., ≥ 0.12 μT occ.	4	0.4 (0.1–1.4)	
			ER+	≥ 0.1 μT res., ≥ 0.12 μT occ.	6	1.6 (0.3–9.9)	

OR, odds ratio; CI, confidence interval; SIR, standardized incidence ratio; res., residential; occ., occupational; ER+, estrogen-receptor-positive; ER–, estrogen-receptor-negative; Ref., reference group with exposure level indicated

The case–control study of residential exposure to magnetic fields and adult cancer in Taiwan (Li *et al.*, 1997) included 2407 histologically confirmed, incident cases of breast cancer in women, of which 1980 were included in the analysis. No association was found between breast cancer and residence less than 50 m from power lines, compared to residence ≥ 100 m from the lines (odds ratio, 1.0; 95% CI, 0.8–1.3; 156 cases). For calculated exposure to magnetic fields, there was no increase in risk among the highest exposure group (> 0.2 μT) (odds ratio, 1.1; 95% CI, 0.9–1.3; 224 cases). [For comments on the limitations of this study see section *(a)*.]

Electric and magnetic fields were considered among a wide variety of environmental and behavioural factors evaluated in a large study seeking reasons for the higher-than-expected breast cancer rates in women resident in the Cape Cod, MA, area in the USA (Coogan & Aschengrau, 1998). The study found a small, non-significant association between breast cancer risk and exposure to magnetic fields. [The Working Group noted that the poor exposure assessment, together with other design flaws, render this study largely uninformative.]

In a population-based case–control study on the effects of exposure to magnetic fields from high-voltage power lines in Sweden, Feychting *et al*. (1998a) also investigated the risk for breast cancer. Men and women who lived within 300 m of a 220- or 400-kV power line for at least one year between 1960 and 1985 were eligible for the study. All male breast cancer cases were included, but only women living in single-family homes were included. Cases were identified from the Swedish National Cancer Registry. A total of 699 female patients matched 1:1 with controls and nine male patients matched 1:8 with controls were included in the analysis. Controls who lived near the same power line as the case with whom they were matched were selected at random from the study base from people who had lived in the power-line corridor for at least one year before the reference date. Controls were matched to cases on age (within five years), sex and parish of residence in the year of the diagnosis. Information from medical records on the estrogen-receptor status of tumours was available for only 102 of the 699 cases. The study showed no overall increase in risk for female breast cancer with increasing estimates of magnetic field exposure; adjusting for socioeconomic status did not change this result. When exposure was defined as the average calculated exposure during the year closest in time to the diagnosis date, with categories of < 0.1 μT, 0.1–0.19 μT and > 0.2 μT, the odds ratio for the highest exposure group was 1.0 (95% CI, 0.7–1.5) for all women. For women aged 50 years or younger, the odds ratio was 1.8 (95% CI, 0.7–4.3); for older women the odds ratio was 0.9 (95% CI, 0.5–1.4). Analyses of cumulative exposure showed a non-significantly elevated risk among women with cumulative exposure ≥ 3.0 μT–years in the six years immediately preceding diagnosis (odds ratio, 1.6; 95% CI, 0.8–3.2; 25 cases). Among estrogen-receptor-positive women, the odds ratio for exposure to ≥ 0.1 μT was 1.6 (95% CI, 0.6–4.1; 17 cases). For estrogen-receptor-positive women aged under 50 years, the odds ratio was 7.4 (95% CI, 1.0–178), based on six exposed cases and one control. For men, a non-significant increase in risk (odds ratio, 2.1; 95% CI, 0.3–14) was observed for

calculated exposure to magnetic fields of ≥ 0.2 μT during the year closest in time to the diagnosis, based on two exposed cases. [The Working Group reiterated the limitations of this study as described in section *(a)*. Additionally, because all the data were obtained from registry and hospital files, no information was available on important risk factors for breast cancer and information on estrogen-receptor status was available for only a few cases.]

The study by Feychting *et al*. (1998a) of breast cancer in Sweden was expanded to combine assessments of residential and occupational exposure (Forssén *et al*., 2000). Unlike the previous breast cancer analysis, which had been limited to single-family homes, this study included all types of dwelling. Cases of breast cancer were identified from the national cancer registry, and one matched control per case was selected at random from the general population. The assessment of occupational exposure was based on census-derived information about occupation that was linked to a job–exposure matrix developed for another study (Floderus *et al*., 1993). For residential exposure to magnetic fields ≥ 0.10 μT for the year closest in time to diagnosis, and occupational exposure < 0.12 μT, the estimated odds ratio was 0.5 (95% CI, 0.1–2.9; 5 cases) and women aged less than 50 years at diagnosis had an odds ratio of 2.4 (95% CI, 0.1–50; 1 case). The highest risk (odds ratio, 7.3; 95% CI, 0.7–78; 4 cases) was for younger women (< 50 years) with higher occupational (≥ 0.12 μT) and residential (≥ 0.1 μT) exposures. [The Working Group noted the very small number of subjects in some subgroups. Occupational exposure was estimated for only 43% of subjects. The study included no information on reproductive risk factors for breast cancer.]

— *Use of electric blankets*

Because of the potential for prolonged exposure to increased electric and magnetic fields, the use of electric blankets has been examined as a risk factor for breast cancer in several recent investigations (Table 28). Vena *et al*. (1991) reported a case–control study that examined the use of electric blankets among 382 women with breast cancer and 439 randomly selected community controls in western New York state in the USA from 1987–89. The study was limited to postmenopausal women and included newly diagnosed, histologically confirmed cases aged 41–85 years admitted to hospitals in the study area between 1987 and 1989. Controls living in the study area were randomly selected from New York drivers' licence records if they were aged under 65 years and from Health Care Financing Administration rosters if they were older. Cases and controls were matched on age. The participation rate was 56% among cases and 46% among controls. The histories of use of electric blankets were obtained through home interviews, using a questionnaire. Information sought included any use of electric blankets in the past 10 years, seasonal pattern of use and mode of use. The study found no significant association with any level of exposure and no dose–response effect. When the results were adjusted for age and education, the odds ratio for breast cancer with use of electric blankets was 0.89 (95% CI, 0.66–12). Further adjustment for risk factors for postmenopausal breast cancer (body mass index, age at first pregnancy,

Table 28. Use of electric blankets and risk for breast cancer in women

Study	Subjects	No. of cases/ controls	Ever use[a]			Daily use			Use through the night[b]			Long-term use[c]		
			OR	No. of cases	95% CI	OR	No. of cases	95% CI	OR	No. of cases	95% CI	OR	No. of cases	95% CI
Vena *et al.* (1991)	Postmenopausal	382/439	0.89	126	0.66–1.2	0.97	NR	0.70–1.4	1.5	68	0.96–2.2	1.4	32	0.77–2.4
Vena *et al.* (1994)	Premenopausal	290/289	1.2	115	0.83–1.7	1.3	84	0.86–1.9	1.4	75	0.94–2.2	1.1	24	0.59–2.1
Vena *et al.* (1995)	Pre- and post-menopausal	672/728	1.1	242	0.85–1.4	1.2	179	0.90–1.5	1.5	143	1.1–1.9	1.2	56	0.81–1.9
Coogan & Aschengrau (1998)[d]	Mostly post-menopausal	259/738	NR	NR	NR	1.0	112	0.7–1.4	NR	112	NR	1.2	23	0.7–2.2
Gammon *et al.* (1998)[e]	< 45 years	1645/1498	1.01	780	0.86–1.2	NR	NR	NR	1.0	630	0.88–1.2	0.96	155	0.74-1.3
	Postmenopausal (45–54 years)	261/250	0.97	143	0.67–1.4	NR	NR	NR	NR	NR	NR	NR	NR	NR
Laden *et al.* (2000)[f]	Premenopausal	95 cases; 41 585 person–years	1.1	42	0.71–1.7	NR	NR	NR	NR	NR	NR	0.88	15	0.49–1.6
	Postmenopausal	797 cases; 233 130 person–years	1.1	354	0.92–1.2	NR	NR	NR	NR	NR	NR	1.1	82	0.85–1.4
Zheng *et al.* (2000)	Pre- and postmenopausal	608/609	0.90	241	0.7–1.1	NR	NR	NR	0.9	147	0.7–1.2	0.8	96	0.6–1.1

OR, odds ratio; CI, confidence interval; NR, not reported

[a] Defined as any use during the last 10 years by Vena; ever use by Gammon

[b] Defined as use through the night by Vena and Zheng; on most of the time by Gammon

[c] Defined as use through the night in-season for 10 years by Vena; longer than 8 years for women aged < 45 years by Gammon; ≥ 20 years by Coogan; longer than 3 years by Zheng; ≥ 10 years for premenopausal women, ≥ 20 years for postmenopausal women by Laden

[d] Sleep with 'electric heating device'

[e] Women aged < 45 years included women from New Jersey, Washington and Atlanta; women aged 45–54 years were from Atlanta only.

[f] Prospective follow-up

number of pregnancies, age at menarche, family history of breast cancer and history of benign breast disease) resulted in an odds ratio of 1.0. There was no trend with increasing number of years of use or with frequency of use. A slightly increased risk was observed for women who reported using electric blankets continuously throughout the night compared with those who never used them (odds ratio adjusted for all risk factors, 1.5; 95% CI, 0.96–2.2; $n = 68$). For the heaviest users who had used electric blankets continuously throughout the night every night during the cold season over the previous 10 years (only 8% of cases and 6% of controls), further analyses showed a slightly increased risk (odds ratio, 1.4; 95% CI, 0.77–2.4). [The Working Group noted that the very low response rates, particularly among controls and the lack of information on the type and age of electric blankets and on other sources of exposure to electric and magnetic fields hamper the interpretation of this study.]

In a second, similar study, Vena *et al*. (1994) again examined use of electric blankets in western New York state, this time among premenopausal women aged 40 years or more. The study included 290 premenopausal women with breast cancer diagnosed between 1986 and 1991 and 289 age-matched controls selected randomly from drivers' licence records in the same geographical area. The response rate was 66% for cases and 62% for controls. The participants were interviewed in their homes using a questionnaire that included questions about use of electric blankets; dietary, medical and reproductive histories, and lifestyle and environmental factors. Use of electric blankets during the previous 10 years was reported by 40% of cases (115 women) and 37% of controls (106 women). After adjustment for age, education, age at first pregnancy, number of pregnancies, family history of breast cancer and other risk factors, the odds ratio for use of an electric blanket at any time in the previous 10 years was 1.2 (95% CI, 0.83–1.7). There was no dose–response relationship between number of years of blanket use and risk of breast cancer. A slight increase in risk was observed among women who used electric blankets daily during the cold season compared with those who never used them (odds ratio, 1.3; 95% CI, 0.86–1.9) and among those who used them continuously throughout the night (odds ratio, 1.4; 95% CI, 0.94–2.2). For the women with the most hours of electric blanket use (continuously throughout the night every night during the cold season for the previous 10 years), the odds ratio was 1.1 (95% CI, 0.59–2.1). [The Working Group considered that this study was limited by the lack of any direct assessment of exposure to electric and magnetic fields, the potential for recall bias and misclassification and the low response rates. Information on the type and age of electric blankets and on other sources of exposure to electric and magnetic fields was also lacking.]

Following a suggestion by Stevens (1995), the two previous studies by Vena *et al*. (1991, 1994) were reanalysed using the combined data (Vena *et al*., 1995). The odds ratio was 1.1 (95% CI, 0.85–1.4) for use of an electric blanket at any time in the previous 10 years, 1.2 (95% CI, 0.90–1.5) for daily use and 1.5 (95% CI, 1.1–1.9) for continuous use throughout the night. Although the results reported for such use showed a significantly increased risk, there was no evidence of a dose–response effect. In the

highest exposure group, which included women who had used electric blankets in the cold season and continuously throughout the night for 10 years, the odds ratio was less elevated, and the confidence interval included the null value (odds ratio, 1.2; 95% CI, 0.81–1.9). Analysis by duration of continuous use throughout the night showed no association with breast cancer except for women who had used the blankets continuously throughout the night for 3–5 years (odds ratio, 2.0; 95% CI, 1.1–3.8).

More recently, in a larger population-based case–control study, Gammon *et al*. (1998) examined use of electric blankets, mattress pads or heated water beds and breast cancer risk. The study included 1645 women under the age of 45 years with breast cancer newly diagnosed between 1990 and 1992 in one of three geographical regions of the United States with tumour registries (Atlanta, GA, five counties in New Jersey and the Puget Sound area in Washington State). The 1498 controls were frequency-matched to cases by five-year age group and geographical area. Also included in the study were 261 postmenopausal women aged 45–55 years and 250 matched controls. The data for postmenopausal women were based solely on Atlanta residents. Although exposure to electric and magnetic fields was not a primary focus of this study, all women were asked about their use of electric bed-heating equipment. Study results indicated that ever having used electric blankets, mattress pads or heated water beds did not increase the risk of breast cancer among premenopausal women (< 45 years old) (odds ratio, 1.0; 95% CI, 0.86–1.2) or postmenopausal women (45–54 years old) (odds ratio, 0.97; 95% CI, 0.67–1.4).

In their study described above, Coogan and Aschengrau (1998) examined the use of electric heating devices during sleep. There was no increase in breast cancer risk associated with regular use (odds ratio, 1.0; 95% CI, 0.7–1.4; 112 cases). [Although the authors did not stratify the results by menopausal status, most of the participants (more than 88%) were postmenopausal.]

A large cohort study, the Nurses' Health Study, in the USA also examined breast cancer and use of electric blankets (Laden *et al*., 2000). The parent study began in 1976, when 121 700 female registered nurses completed a postal questionnaire. Diagnoses of breast cancer were reported on follow-up questionnaires and confirmed by medical records (for most cases). A question on use of electric blankets was added in 1992. The prospective (1992–96) analysis was restricted to 78 614 women not diagnosed with cancer before 1992 who had answered this question (954 breast cancer cases). The retrospective analyses (1976–92) included 85 474 women who had answered this question (2426 breast cancer cases) and were cancer free at the start of the study. The reported relative risks for ever having used electric blankets were 1.1 (95% CI, 0.95–1.2; 426 cases) and 1.0 (95% CI, 0.92–1.1; 1041 cases), based on prospective and retrospective follow-up, respectively. After adjusting for known risk factors for the disease, there was little indication of a trend in risk associated with number of years of electric blanket use. Similar results were obtained for pre- and postmenopausal women and for women with estrogen-receptor-positive breast cancer.

Zheng *et al.* (2000) analysed data from a case–control study of breast cancer in Connecticut, USA, between 1994 and 1997. The study included two separate sources of cases (31–85 years old) and controls. One group included incident cases identified from the surgical pathology department of Yale-New Haven Hospital (432/561; 77% participation) and hospital controls who had undergone breast surgery for benign breast disease or had histologically confirmed normal tissue (404/569; 71% participation). A second group comprised cases resident in Tolland County identified through the Connecticut Tumor Registry (176; 74% participation). The controls for this group were selected by random-digit dialling (152; 64% participation) or, for those over 65 years of age, from Health Care Administration records (53; 54% participation). Information on use of electric blankets and other electrical appliances was obtained by interviewing the participants. Around 40% of cases and controls reported regular use of electric blankets and the odds ratio was 0.9 (95% CI, 0.7–1.1). The risk did not vary with age at first use, duration of use, or menopausal or estrogen-receptor status and was the same for subjects who used electric blankets regularly throughout the night. Similarly unremarkable results were obtained for use of other common domestic appliances.

(*d*) *Other cancers*

In the 1996 Finnish cohort study, described in section *(a)*, Verkasalo *et al.* (1996) examined the relationship between cancer risk and exposure to magnetic fields from high-voltage power lines. Overall, 8415 cancer cases were identified (4082 were men). No association was found between cumulative exposure and the risk for all cancers (SIR, 0.98; 95% CI, 0.96–1.0 per μT–year) or for any specific type of cancer studied. Only for skin melanoma was the risk slightly increased throughout the three highest cumulative exposure categories: SIRs were 0.87 (95% CI, 0.54–1.3; 21 cases), 1.5 (95% CI, 0.98–2.1; 28 cases), 1.5 (95% CI, 0.69–2.7; 10 cases) and 1.2 (95% CI, 0.48–2.5; 7 cases) for exposure to fields of 0.20–0.39 μT, 0.40–0.99 μT, 1.0–1.99 μT and ≥ 2.0 μT, respectively. The SIR for multiple myeloma showed a marginally significant increase in men (SIR, 1.2; 95% CI, 1.0–1.5 per μT–year) and a non-significant decrease in women (SIR, 0.87; 95% CI, 0.57–1.3 per μT–year). For colon cancer, the risk was marginally increased in women (SIR, 1.2; 95% CI, 1.0–1.3 per μT–year), but not in men. [For the comments of the Working Group on this study, see section *(a)*.]

Finally, in a population-based study of 175 men with prostate cancer aged 40–69 years and 258 controls, Zhu *et al.* (1999) reported a relative risk of 1.4 (95% CI, 0.9–2.2) for ever having used an electric blanket or heated water bed, but the risk did not appear to increase with increasing duration of use.

2.3.2 *Occupational exposure to ELF electric and magnetic fields*

(*a*) *Proportionate mortality or incidence studies*

Proportionate mortality studies should be interpreted with caution because apparent mortality excesses, particularly those of moderate size, can be the result of a deficit of mortality from other causes (Monson, 1990).

The studies described below were designed mainly for generating hypotheses, especially by use of record linkage with routinely collected data.

In early studies on the relation between electric and magnetic fields and cancer, exposure to electric and magnetic fields was inferred from the job title only, on the assumption that 'electrical workers' were exposed to higher than background electric and magnetic fields. The first list of 'electrical' occupations which supposedly entailed high exposure to electric and magnetic fields was established by Milham (1982). This list, or a modified version thereof, was used as the basis for exposure assessment in subsequent studies. The job titles most generally considered to denote 'electrical' occupations were electronic technicians and engineers, radio and telegraph operators, electricians, power and telephone linemen, television and radio repairers, power-station operators, aluminium workers, welders (see IARC, 1990) and flame cutters, and motion-picture projectionists.

Milham (1982) conducted a study in 1950–79 based on death certificates in Washington State, USA, for white men ≥ 20 years of age. The study was later updated for the period 1950–82 (Milham, 1985b). Employment in one of nine electrical occupations as listed on the death certificate, was used as a surrogate for exposure to electric and magnetic fields. Significantly elevated proportionate mortality ratios (PMRs) were observed for all leukaemia (PMR, 1.4 [95% CI, 1.1–1.6]; 146 cases), acute leukaemia (PMR, 1.6 [95% CI, 1.3–2.1]), malignant brain tumours (PMR, 1.2 [95% CI, 1.0–1.5]) and other lymphomas (PMR, 1.6 [95% CI, 1.2–2.2]), as well as malignant tumours of the pancreas (PMR, 1.2 [95% CI, 1.0–1.4]) and lung (PMR, 1.1 [95% CI, 1.1–1.2]).

In a study in Los Angeles County, USA, Wright *et al*. (1982) looked at incident cases of leukaemia that occurred from 1972–79 among white men employed in one of 11 electrical occupations. The proportionate incidence ratios (PIRs) were 1.3 [95% CI, 0.9–1.8] for all leukaemia (35 cases), 1.7 [95% CI, 1.1–2.6] for acute leukaemia and 2.1 [95% CI, 1.3–3.1] for acute myeloid leukaemia.

To evaluate leukaemia mortality in men employed in one of 10 electrical occupations, McDowall (1983) re-analysed data routinely collected in England and Wales for a report on occupational mortality in 1970–72. On the basis of all deaths in men aged 15–74 years, the PMRs of these occupations taken together were not significantly different from those expected, either for all leukaemia (PMR, 0.98; 85 cases) or for any specific subtype of leukaemia.

To evaluate leukaemia incidence in electrical occupations further, Coleman *et al*. (1983) used the routinely collected records of the South Thames Cancer Registry in England to calculate the proportionate registration ratio (PRR) for leukaemia for the

period 1961–79 for men aged 15–74 employed in one of 10 electrical occupations. Eight of the 10 occupations showed an excess of all leukaemia with a significantly increased PRR of 1.2 ($p < 0.05$) for all 10 electrical occupations taken together (113 cases). There was no overall excess of chronic myeloid leukaemia, but non-significant excesses occurred in acute lymphoblastic (PRR, 1.5), chronic lymphocytic (PRR, 1.3) and acute myeloid (PRR, 1.2) leukaemia.

The death certificates of men aged ≥ 20 years were used in Wisconsin, USA, during 1963–78 to analyse leukaemia deaths in relation to 10 electrical occupations (Calle & Savitz, 1985). The PMR for all leukaemia in electrical occupations was 1.0 ([95% CI, 0.82–1.3]; 81 cases) and that for acute leukaemia was 1.1 [95% CI, 0.81–1.5].

Data from five descriptive studies that examined either the PMR (Milham, 1982; McDowall, 1983; Calle & Savitz, 1985; Milham, 1985b) or the PIR (Wright *et al*., 1982; Coleman *et al.*, 1983) for leukaemia in workers in electrical occupations, i.e. workers with suspected high exposure to ELF electric and magnetic fields were pooled by Stern (1987). This data set which included a total of 449 cases of all leukaemia, yielded a relative risk of 1.1 [95% CI, 1.0–1.3] for all occupations combined. For the subgroups of acute leukaemia and acute myeloid leukaemia, the relative risk estimates were 1.4 [95% CI, 1.2–1.6] and 1.4 [95% CI, 1.1–1.7], respectively.

Death certificates from 1950–84 for men aged ≥ 20 years were used in a study conducted in British Columbia, Canada (Gallagher *et al*., 1990). The PMR for all leukaemia in men working in one of nine electrical occupations was [1.1; 95% CI, 0.8–1.4] (65 cases). Using the same data, the PMR for brain cancer in workers employed in the same nine occupations was 1.3 (95% CI, 0.93–1.6; 55 cases) for men aged 20–65 years (Gallagher *et al*., 1991).

In a study on mortality data for white men > 15 years old collected from 14 states in the USA for one or more years from 1979–85, the PMR for all leukaemia in 11 electrical occupations was 1.2 (95% CI, 1.0–1.4; 183 observed) and 1.1 (95% CI, 0.85–1.5) for acute myeloid leukaemia (Robinson *et al*., 1991).

To evaluate PRRs of cancer among electrical workers, Fear *et al*. (1996) used routinely collected data reported to the national cancer registration scheme in England during 1981–87 on more than 1 million cancers in individuals aged 20–74 years. The analysis, however, was based on only 36% of registrations for which valid occupational information was provided. Twelve job groups out of a total of 194 were identified as electrical occupations. For these job groups combined, and for both sexes jointly, significantly raised risks were seen for all brain and meningeal cancers combined (PRR, 1.2; 95% CI, 1.0–1.3; 281 cases), malignant brain cancer alone (PRR, 1.2; 95% CI, 1.0–1.4; 204 cases), all leukaemias combined (PRR, 1.2; 95% CI, 1.1–1.4; 217 cases) and acute myeloid leukaemia alone (PRR, 1.3; 95% CI, 1.0–1.6; 80 cases). For several types of cancer, most notably malignant brain cancer and acute myeloid leukaemia, the increased PRRs were most evident in men < 65 years old.

A study in São Paulo, Brazil, based on death certificates obtained from a sample of electricity utility workers in 1975–85 was conducted by Mattos and Koifman (1996).

The PMR in the group of workers expected to have been exposed to strong electric and magnetic fields was increased for brain cancer (ICD-9 191, 192) (PMR, 3.8; 95% CI, 1.0–9.7), Hodgkin disease (PMR, 5.6; 95% CI, 1.1–16) and bladder cancer (PMR, 4.2; 95% CI, 1.4–9.7).

(*b*) *Cohort studies*

Table 29 presents selected results of studies that have looked at occupational exposure to static and ELF magnetic fields and leukaemia, brain cancer and breast cancer, the malignancies on which most attention has focused. A few studies have reported excesses of other cancers such as malignant melanoma, non-Hodgkin lymphoma and lung cancer for which the majority of other studies could not reproduce the findings. These studies are not shown in the Table but are described in the text.

(i) *Workers exposed to strong static magnetic fields*

There are certain industries (aluminium reduction (see IARC, 1984, 1987a) and production of chlorine by electrolysis in chloralkali plants) in which workers are exposed to static magnetic fields, usually created by strong rectified alternating current. The aluminium reduction process involves exposure to static magnetic fields from direct currents passing through the anodes during electrolysis (reduction). The magnetic field to which the workers are exposed has been estimated to be between 4 and 50 mT (Kowalczuk *et al*., 1991). The process also involves potential exposure to a mixture of volatiles from coal-tar pitch (see IARC, 1985, 1987b) and petroleum coke.

Barregård *et al*. (1985) studied cancer mortality and cancer incidence in a group of 157 male workers at a Swedish chloralkali plant. The employees had all worked regularly or permanently for at least one year during the period 1951–83 in the cell room where the electrolysis process took place. These workers had been exposed to strong static magnetic fields (average, 14 mT). The investigators reported no excess incidence of, or mortality from, cancer.

In a cohort study of 27 829 aluminium workers employed for ≥ 5 years between 1946 and 1977 in 14 reduction plants in the USA, Rockette and Arena (1983) reported indications of higher than expected mortality from pancreatic, genitourinary and lymphohaematopoietic cancers. Deaths from lymphohaematopoietic cancer were not confined to one subcategory of disease, or to one industrial process. [The Working Group noted that these results cannot be interpreted in relation to exposure to magnetic fields.]

A cohort study was carried out in British Columbia, Canada, of 4213 workers with ≥ 5 years of work experience at an aluminium reduction plant between 1954 and 1985 (Spinelli *et al*., 1991). The static magnetic fields usually generated in the plant were approximately 1 mT. The potential exposure to magnetic fields and to coal-tar pitch volatiles was determined for each job by industrial hygienists using a job–exposure matrix. The standardized mortality ratio (SMR) in the total cohort was 2.2 (90% CI, 1.2–3.7) for tumours of the brain and central nervous system (ICD-9 191, 192) and 1.8

Table 29. Cohort studies of leukaemia, brain and breast cancer in occupational groups with assumed or documented exposure to static or ELF magnetic fields

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
Sweden (Einhorn *et al*., 1980; Wiklund *et al*., 1981)	Telephone operators SIR (14 480; 14 180 women and 300 men), 1960 census; 1961–73	Not estimated	Leukaemia	12	1.0	[0.6–1.8][b]	Unadjusted for potential occupational confounders
Sweden (Olin *et al*., 1985)	Electrical engineers SMR (1243 men), 1930–59; 1930–79	Not estimated	Leukaemia Brain	2 2	0.9 1.0	(0.1–3.2) (0.1–3.7)	Unadjusted for potential occupational confounders
Sweden (Vågerö *et al*., 1985)	Telecommunications equipment workers SIR (2914; 2047 men and 867 women), 1956–60; 1958–79	Not estimated	**Men** Nervous system **Women** Breast cancer	 5 7	 1.0 0.6	 (0.3–2.3) (0.3–1.3)	Unadjusted for potential occupational confounders
Sweden (Törnqvist *et al*., 1986)	Power linesmen SIR (3358 men), 1960 census; 1961–79	Not estimated	Leukaemia Nervous system	10 13	1.3 1.5	(0.7–2.1) (0.9–2.4)	90% CI. Unadjusted for potential occupational confounders
	Power station operators SIR (6703 men), 1960 census; 1961–79	Not estimated	Leukaemia Nervous system	16 17	1.0 1.0	(0.6–1.5) (0.6–1.5)	90% CI. Unadjusted for potential occupational confounders
Sweden (Törnqvist *et al*., 1991)	Workers in electrical occupations SIR (133 687 men), 1960 census; 1961–79	Median during working hours: < 0.04–16.5 μT (50 measurements)	Leukaemia Brain tumours	334 250	SIR slightly raised SIR close to unity		Unadjusted for potential confounders

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
USA (Garland *et al*., 1990)	US Navy personnel SIR (> 4 million person–years white men), 1974–84; 1974–84	Not estimated	**Leukaemia** All cohort Electrician's mate	 102 7	 0.9 2.4	 (0.8–1.1) (1.0–5.0)	Unadjusted for potential occupational confounders
Finland (Juutilainen *et al*., 1990)	Male industrial workers SIR [number not given] 1970 census; 1971–80	No measurements	**Leukaemia** No exposure Possible exposure Probable exposure **Brain tumours** No exposure Possible exposure Probable exposure	 117 94 10 204 149 13	 1.0 1.4 1.9 1.0 1.3 1.3	 (baseline) (1.1–1.8) (1.0–3.5) (baseline) (1.0–1.6) (0.7–2.3)	Unadjusted for potential confounders
Norway (Tynes & Andersen, 1990)	Workers in electrical occupations SIR (37 952 men), 1960 census; 1961–85	No measurements	Male breast	12	2.1	(1.1–3.6)	Unadjusted for potential confounders
Norway (Tynes *et al*., 1992)	Workers in electrical occupations SIR (37 945 men), 1960 census; 1961–85	No measurements	Leukaemia AML CLL CML Brain	107 38 27 19 119	1.1 1.3 0.97 1.5 1.1	(0.89–1.3) [0.88–1.7][b] (0.64–1.4) (0.90–2.3) (0.90–1.4)	Unadjusted for potential confounders

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
USA (Matanoski *et al*., 1991)	Telephone workers SIR (4547 male cable splicers, 9561 central office technicians), 1976–80; 1976–80	Personal monitoring of a sample of workers	Male breast Cable splicer Central office technicians	 0 2	 – 6.5	 – (0.79–24)	Electromechanical switches environment in central office
Canada, British Columbia (Spinelli *et al*., 1991)	Aluminium reduction plant workers SIR (4213 men), 1954–85; 1954–85	No personal measurements (magnetic fields around 1 mT generated during industrial process)	Leukaemia Brain	3 8	0.76 1.9	[0.15–2.2][b] [0.84–3.8][b]	No significant association with estimated cumulative exposure to strong static magnetic fields (values not given)
Denmark (Guénel *et al*., 1993b)	Workers in electrical occupations SIR (255 000; 172 000 men, 83 000 women), 1970 census; 1970–87	Continuously above 0.3 μT	**Men** Leukaemia – acute – other Brain and nervous system Breast **Women** Leukaemia Brain and nervous system Breast	 39 16 23 23 2 2 9 55	 1.6 1.6 1.7 0.69 1.4 0.56 1.2 0.88	 (1.2–2.2) (0.90–2.6) (1.1–2.5) (0.44–1.0) (0.16–4.9) (0.07–2.0) (0.56–2.3) (0.68–1.2)	Unadjusted for potential confounders

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
		Intermittently above 0.3 μT	**Men**				
			Leukaemia	282	0.94	(0.84–1.1)	
			– acute	119	1.0	(0.84–1.2)	
			– other	164	0.90	[0.77–1.1][b]	
			Brain and nervous system	339	0.94	(0.85–1.1)	
			Breast	23	1.2	(0.77–1.8)	
			Women				
			Leukaemia	94	0.92	(0.75–1.1)	
			– acute	47	0.93	(0.70–1.2)	
			– other	47	0.91	(0.68–1.2)	
			Brain and nervous system	198	1.1	(0.93–1.2)	
			Breast	1526	0.96	(0.91–1.0)	
Sweden (Floderus *et al*., 1994)	Male railroad workers SIR [not given], 1960 census; 1961–79	Spot measurements	**All leukaemia**				
			Engine drivers				
			1961–69	6	1.6	(0.7–3.6)	
			1970–79	8	1.0	(0.5–2.1)	
			All railway workers				
			1961–69	17	1.2	(0.7–1.9)	
			1970–79	26	0.9	(0.6–1.3)	
			CLL				
			Engine drivers				
			1961–69	4	2.7	(1.0–7.4)	
			1970–79	4	1.1	(0.4–2.9)	

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
			Breast cancer				
			Engine drivers				
			1961–69	2	8.3	(2.0–34)	
			1970–79	0	0.0	(0.0–6.0)	
			Railway workers				
			1961–69	4	4.3	(1.6–12)	
			1970–79	0	0.0	(0.0–1.6)	
			Brain tumours				
			Engine drivers				
			1961–69	8	1.1	(0.6–2.2)	
			1970–79	10	0.9	(0.5–1.6)	
			Railway workers				
			1961–69	31	1.2	(0.8–1.6)	
			1970–79	39	0.9	(0.7–1.3)	
Norway (Tynes *et al*., 1994a)	Workers in 8 power companies SIR (5088 men), 1920–85; 1953–91	Spot measurements and assessment of cumulative exposure to ELF magnetic fields	**Leukaemia**	11	0.90	(0.45–1.6)	
			Duration of employment				
			< 10 years	1	0.56	NR	
			10–29 years	6	1.2	NR	
			≥ 30 years	4	0.73	NR	
			Cumulative exposure				
			< 5 μT–years	2	0.95	NR	
			5–35 μT–years	4	0.74	NR	
			> 35 μT–years	5	1.0	NR	

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
			Brain tumours	13	0.88	(0.47–1.5)	
			Duration of employment				
			< 10 years	3	0.91	NR	
			10–29 years	7	1.0	NR	
			≥ 30 years	3	0.65	NR	
			Cumulative exposure				
			< 5 μT–years	6	1.8	NR	
			5–35 μT–years	5	0.71	NR	
			> 35 μT–years	2	0.44	NR	
USA (Savitz & Loomis, 1995)	Utility workers SMR (138 905 men), 1950–86; 1950–88	Job–exposure matrix based on measurements of magnetic fields	*Magnetic fields (μT–years)*				
			Leukaemia				
			0.6–< 1.2	34	1.0	(0.66–1.6)	
			1.2–< 2.0	35	1.1	(0.70–1.8)	
			2.0–< 4.3	27	0.95	(0.56–1.6)	
			≥ 4.3	14	1.1	(0.57–2.1)	
			AML				
			0.6–< 1.2	12	1.3	(0.59–2.8)	
			1.2–< 2.0	7	0.94	(0.36–2.4)	
			2.0–< 4.3	5	0.72	(0.24–2.2)	
			≥ 4.3	5	1.6	(0.51–5.1)	
			CLL				
			0.6–< 1.2	8	1.3	(0.49–3.6)	
			1.2–< 2.0	13	2.0	(0.77–5.1)	
			≥ 2.0	5	0.55	(0.17–1.8)	

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
			Brain cancer				
			0.6–< 1.2	34	1.6	(0.99–2.6)	
			1.2–< 2.0	26	1.5	(0.84–2.6)	
			2.0–< 4.3	27	1.7	(0.92–3.0)	
			≥ 4.3	16	2.3	(1.2–4.6)	
Sweden (Alfredsson *et al*., 1996)	Male railway engine drivers and conductors SIR (9738), 1976–90; 1976–90	Not estimated	Leukaemia	20	1.2	(0.7–1.9)	
			Lymphocytic leukaemia				
			All ages	14	1.6	(0.9–2.6)	
			20–64 years	10	2.3	(1.3–3.2)	
Denmark (Johansen & Olsen, 1998)	Utility workers SIR (32 006; 26 135 men, 5871 women), 1908–93; 1968–93	24-h measurements and job–exposure matrix for ELF magnetic fields	**Men**				
			All leukaemias	60	0.92	(0.7–1.2)	
			acute	20	0.87	(0.5–1.4)	
			chronic lymphoblastic	27	0.92	(0.6–1.3)	
			chronic myeloid	6	0.65	(0.2–1.4)	
			Brain	57	0.79	(0.6–1.0)	
			Breast	2	0.50	(0.1–1.8)	
			Women				
			All leukaemias	3	0.50	(0.1–1.5)	
			Brain	15	1.3	(0.7–2.2)	
			Breast	96	1.1	(0.9–1.3)	
China (Petralia *et al*., 1998)	Female population in urban Shanghai SIR (population size not given), 1980–84; 1980–84	Exposure estimated from occupation at diagnosis	*Breast*				
			Exposure probability				
			Low	683	1.0	(0.9–1.0)	
			Medium	72	1.1	(0.9–1.4)	
			High	72	0.9	(0.7–1.2)	

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
			Exposure level				
			Low	602	1.0	(0.9–1.1)	
			Medium	0		–	
			High	130	1.0	(0.8–1.2)	
			Any exposure	827	1.0	(0.9–1.0)	
Sweden (Floderus *et al*., 1999)	Large proportion of national working population SIR (1 596 959 men and 806 278 women), 1970 census; 1971–1984	Measurements and job–exposure matrix; upper exposure tertile (men = 0.116 μT; women = 0.138 μT) versus all subjects	**Men**				
			All leukaemias	648	1.1	(1.0–1.2)	
			AML	199	1.1	(0.9–1.4)	
			CML	116	1.1	(0.8–1.4)	
			ALL	32	1.5	(0.9–2.7)	
			CLL	301	1.1	(0.9–1.2)	
			Brain	1100	1.1	(1.0–1.2)	
			Breast	37	1.2	(0.7–1.9)	
			Women				
			All leukaemias	263	1.1	(1.0–1.4)	
			AML	107	1.1	(0.8–1.5)	
			CML	57	0.8	(0.6–1.2)	
			ALL	12	1.1	(0.5–2.4)	
			CLL	87	1.7	(1.2–2.4)	
			Brain	598	0.9	(0.8–1.1)	
			Breast	4866	1.1	(1.0–1.1)	

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
Norway (Kliukiene *et al*., 1999)	Female population of country SIR (1 177 129), 1960, 1970, 1980 censuses; 1961–92	Measurements and job–exposure matrix	*Breast* **Work hours** 1–899 900–999 1000–1999 ≥ 2000 **Exposure μT–years** 0.1–0.8 0.9–1.4 1.5–3.0 > 3.0	 NR NR NR NR NR NR NR NR	 1.00 1.07 1.08 1.14 1.00 1.07 1.12 1.08	 (baseline) (1.03–1.12) (1.07–1.17) (1.01–1.16)	Adjusted for age, time-period and socioeconomic status
Italy (Pira *et al*., 1999)	Geothermal power plant workers SMR (3946 men), 1950–90; 1950–90	No formal evaluation	Leukaemia Brain	8 11	0.79 1.2	(0.34–1.6) (0.57–2.1)	
Norway (Rønneberg *et al*., 1999)	Aluminium smelter workers; production worker subcohort SIR (2888 men), 1953–93	Measurements and job–exposure matrix	Brain	7	0.71	(0.29–1.5)	Strong static magnetic fields
England and Wales (Harrington *et al*., 2001)	Electricity generation and transmission workers, SMR (72 954 men and 11 043 women); 1973–82; 1973–97	Job–exposure matrix based on measurements of magnetic fields	**Leukaemia** *SMR*: Total *Period from hire* 0–9 years 10–19 years 20–29 years ≥ 30 years	 111 6 34 37 34	 0.84 0.51 1.1 0.91 0.71	 (0.69–1.0) (0.19–1.1) (0.73–1.5) (0.64–1.3) (0.49–1.0)	

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)		Comments
			RR: cumulative exposure (μT–years)				
			0–2.4	60	1.0		
			2.5–4.9	18	1.5	(0.87–2.5)	
			5.0–9.9	20	0.99	(0.59–1.7)	
			10.0–19.9	17	0.96	(0.55–1.7)	
			≥ 20.0	9	1.4	(0.68–2.8)	
Switzerland (Minder & Pfluger, 2001)	Railway workers, SMR (18 070 men), 1972–93; 1972–93	Measurements at the workplaces with estimates of historical exposure	**Leukaemia**				
			Station masters	6	1.0	(baseline)	
			Line engineers	19	2.4	(0.97–6.1)	
			Shunting yard engineers	3	2.0	(0.50–8.1)	
			Train attendants	9	1.1	(0.39–3.1)	
			μT–years				
			0–4.9	6	1.0	(baseline)	
			5–74.9	9	0.78	(0.72–2.2)	
			≥ 75	22	1.6	(0.64–4.2)	

Table 29 (contd)

Country (reference)	Population, design (number), recruitment period; follow-up period	Assessment of exposure to ELF magnetic fields[a]	Cancer	No. of cases	Relative risk (95% CI)	Comments
			Brain tumours			
			Station masters	3	1.0 (baseline)	
			Line engineers	4	1.0 (0.23–4.6)	
			Shunting yard engineers	5	5.1 (1.2–21)	
			Train attendants	11	2.7 (0.75–9.6)	
			μT–years			
			0–4.9	1	1.0 (baseline)	
			5–74.9	11	2.8 (0.35–23)	
			≥ 75	11	2.4 (0.29–19)	

AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; SMR, standardized mortality ratio; SIR, standardized incidence ratio; NR, not reported

[a] The studies by Spinelli *et al.* (1991) and Rønneberg *et al.* (1999) deal with exposure to static magnetic fields.

[b] Calculated by the Working Group

(90% CI, 0.8–3.3) for leukaemia (ICD-9, 204–208). For cancer incidence ascertained from 1970 onwards, the SIR was 1.9 (90% CI, 0.97–3.5) for brain cancer (ICD-9 191), and 0.76 (90% CI, 0.21–2.0) for leukaemia. However, no individual cause of cancer death or incident cancer was related to cumulative exposure to magnetic fields, as estimated from the job–exposure matrix.

Rønneberg *et al*. (1999) studied cancer incidence in a population composed of 2647 male short-term workers and two cohorts of men employed for at least four years (2888 production workers and 373 maintenance workers) at an aluminium smelter in Norway. Data on all men first hired at an hourly wage and with at least six months of continuous employment were obtained from company files dating back to 1946. Of the 5962 men who initially satisfied the inclusion criteria, six had died before the observation period started in 1953 and 48 were lost to follow-up. The remaining 5908 men were linked to the files of the Norwegian Cancer Registry and followed up from 1953 (or date of first employment) until date of death or emigration, or the end of 1993. Exposure to magnetic fields, ranging from 2–10 mT for static magnetic fields and from 0.3–10 μT for time-varying magnetic fields (mainly 50–300 Hz), was estimated from a survey of other Norwegian smelters (Thommesen & Bjølseth, 1992). Cumulative exposure for each worker was calculated as the product of the estimated exposure intensity and duration, summed for all jobs held at the smelter. Overall, the cancer incidence was not elevated in any of the three cohorts when compared with the expected incidence calculated on the basis of the age- and calendar year-specific cancer incidence of all men in Norway applied to the person–years at risk among cohort members. There was no association observed in the entire cohort of 2888 production workers between level of exposure to static magnetic fields or ELF magnetic fields and cancers of the brain or lymphatic and haematopoietic tissue, on the basis of seven and 32 observed cases, respectively. No excess of the latter cancers was observed among the highly exposed power-plant and rectifier workers of the production cohort, where two cases were observed as against 1.9 expected. Separate estimates of risk for leukaemia were not given.

(ii) *Workers exposed to electric and magnetic fields (not strong static magnetic fields)*

Following the detection of four cases of leukaemia among telephone operators in the city of Gothenburg, Sweden during 1969–74, a retrospective record linkage study of the entire national population was undertaken (Einhorn *et al*., 1980; Wiklund *et al*., 1981). A total of 14 480 telephone operators (14 180 women and 300 men) were identified from the 1960 population census in Sweden. Data linkage with the files of the nationwide Swedish Cancer Registry for the period 1961–73 revealed a total of 12 cases of leukaemia when 11.7 cases were expected on the basis of national age- and sex-specific incidence rates of the disease. [The Working Group noted that no effort was made by the authors to estimate potential job-related exposure to ELF electric and magnetic fields.]

In a study in Sweden based on a large-scale linkage of occupational data from the 1960 census and data from the national cancer registry for the years 1961–73, Vågerö and Olin (1983) investigated 54 624 men and 18 478 women, aged 15–64 years, working in the electronics or electrical manufacturing industry. They found significantly increased risks, of 15% in men and 8% in women, for cancer at all sites combined, compared with those of the working population in general. These increases were due mainly to significant increases in the risk for cancers of the pharynx, larynx and lung, and for malignant melanoma among men, and cervical cancer among women.

In a mortality study by Olin *et al*. (1985) of 1254 male electrical engineers, all of whom had graduated from one university in Sweden during 1930–59, 11 were lost to follow-up. The remaining 1243 cohort members were followed until date of death or the end of 1979. When compared with the age- and calendar time-adjusted mortality rates of the general Swedish male population, the SMR for cancer at all sites combined was 0.5 (95% CI, 0.3–0.7) on the basis of 24 observed cases. Three deaths from malignant melanoma were observed as opposed to 0.9 expected (SMR, 3.2; 95% CI, 0.7–9.4), and two deaths from leukaemia occurred as opposed to 2.3 expected (SMR, 0.9; 95% CI, 0.1–3.2). [The Working Group noted that no effort had been made by the authors to estimate potential job-related exposure to ELF electric and magnetic fields.]

Vågerö *et al*. (1985) evaluated cancer incidence in 2918 subjects (2051 men, 867 women) employed for at least six months during the period 1956–60 by a Swedish company at one of three worksites producing telecommunications equipment. All but four subjects, for whom personal data could not be verified, were linked to the files of the Swedish Cancer Registry for the period 1958–79. The observed numbers of cancers among cohort members were compared with the expected numbers, calculated on the basis of age-, sex- and calendar year-specific incidence rates for the entire Swedish population. Overall, 102 cancers were observed among men and 37 among women, yielding SIRs of 1.03 (95% CI, 0.8–1.2) and 0.98 (95% CI, 0.7–1.4), respectively. An increased risk for malignant melanoma was seen in both men (SIR, 2.5; 95% CI, 1.1–4.9; 8 cases) and women (SIR, 2.8; 95% CI, 0.8–7.2; 4 cases); the highest risk estimates were seen for departments associated with soldering work, but this observation was based on a total of only four observed cases in men and two in women (SIR, 3.9; 95% CI, 1.4–8.5) (both sexes combined). Two cases of Brill-Symmer disease (a nodular lymphoma) were seen in men as opposed to 0.1 expected. [The Working Group noted that no effort was made by the authors to estimate the potential job-related exposure to ELF electric and magnetic fields.]

From the 1960 population census in Sweden, Törnqvist *et al*. (1986) identified a total of 3358 male power linemen and 6703 male power-station operators in the electric power industry, who were all aged 20–64 years at the time of the census. Cohort members were linked to the files of the national Swedish Cancer Registry and followed up for cancer incidence until the end of 1979. The observed numbers of cancers were compared with the expected numbers, calculated on the basis of age-, county- and calendar year-specific cancer incidence rates for all men classified as blue collar

workers by the census. Overall, 236 cancers were observed among power linemen and 463 cancers among power station operators, yielding SIRs of 1.1 (90% CI, 1.0–1.2) and 1.0 (90% CI, 0.9–1.0), respectively. For none of the specific cancer sites included in the analysis did the lower confidence limit exceed unity. The SIR for leukaemia among power linemen was 1.3 (90% CI, 0.7–2.1) and that among power station operators was 1.0 (90% CI, 0.6–1.5) on the basis of 10 and 16 observed cases, respectively. None of the major subgroups of leukaemia showed an excess risk in either occupational group. The SIR estimate for tumours of the nervous system was 1.5 (90% CI, 0.9–2.4) among power linemen and 1.0 (90% CI, 0.6–1.5) among power-station operators on the basis of 13 and 17 observed cases, respectively. [The Working Group noted that no effort was made by the authors to estimate potential job-related exposure to ELF electric and magnetic fields.]

This cohort was later extended (Törnqvist *et al*., 1991) to include all men in Sweden aged 20–64 who had worked in one of 11 electrically related occupations according to the job title recorded in the 1960 census, giving a total of 133 687 [or 7% of all Swedish working men]. In addition, the magnetic field exposure was estimated by five occupational hygienists, according to Swedish working conditions in the selected occupational categories. However, these estimates were based on only 50 measurements conducted over 4–8 h (except for two measurements made over nearly 18 h). A total of 334 cases of leukaemia was observed during 1961–79 which was only slightly in excess of the expected number [figure not stated] calculated on the basis of the incidence rates of cancer among all Swedish working men. Similarly, a total of 250 cases of brain tumour were identified which was approximately equal to the expected number [figure not stated]. Although significant, or marginally significant, positive associations were seen between one or more of the occupations under consideration (or industry subgroups thereof) and specific subtypes of leukaemia (acute myeloid, chronic myeloid, acute lymphoblastic, chronic lymphocytic, all subtypes combined) or brain tumour (glioma, glioblastoma, all subtypes combined), the authors concluded that no homogeneous pattern of increased risks associated with occupations for which there is presumed to be exposure to high ELF magnetic fields, was found. The authors noted that the occupation of the study subjects was known only on the census date in 1960, and that the estimates of ELF electric and magnetic fields were based on a small number of measurements.

De Guire *et al*. (1988) carried out a cohort study of 9590 workers employed between 1976 and 1983 in the Montreal plants of a telecommunications company. During the study period, 10 cases of malignant melanoma of the skin were diagnosed among men and none among women. Using reference rates for malignant melanomas in the Greater Montreal area during the same period, the SIR for men was 2.7 (95% CI, 1.3–5.0). [If the total cohort is considered, the expected number of cases is five (combined 95% CI, 1.1–3.7)] [The Working Group noted that the study was conducted in response to the observation of a cluster of melanomas among workers at one plant. No data were available on job titles or on specific types of exposure among these workers.]

In a cohort study of US Navy personnel (4 072 502 person–years), 102 cases of leukaemia were diagnosed among men on active duty in 1974–84 (Garland *et al*., 1990). The overall incidence of leukaemia was close to that of the population of the United States. In the analysis by occupation, seven cases were reported among electrician's mates (111 944 person–years) with possible high exposure to 60-Hz electric and magnetic fields, yielding an increased risk for leukaemia in this group (SIR, 2.4; 95% CI, 1.0–5.0). No increased risk for leukaemia was observed in other occupational groups, in particular in naval workers with probable exposure to electric and magnetic fields at frequencies higher than 60 Hz. [The Working Group noted that there was no assessment of exposure to electric and magnetic fields by occupation.]

From the 1970 population census in Finland, Juutilainen *et al*. (1990) selected all Finnish men, aged 25–64 years, during the period 1971–80 who were classified as industrial workers according to their self-reported occupation. The occupations were grouped into three exposure categories according to the probability of exposure to ELF magnetic fields, i.e. no exposure, possible exposure and probable exposure. Cohort members were linked with the Finnish mortality files for determination of vital status through 1980 and to the files of the Finnish Cancer Registry for verification of incident cases of leukaemia and tumours of the central nervous system during the period 1971–80. Using all industrial workers with no exposure to ELF magnetic fields as the comparison group, the authors found relative risks for leukaemia of 1.4 (95% CI, 1.1–1.8; 221 cases) and 1.9 (95% CI, 1.0–3.5) for workers with possible and probable exposure, respectively, and, for brain tumour, the relative risks were 1.3 (95% CI, 1.0–1.6) and 1.3 (95% CI, 0.7–2.3), respectively.

From the 1960 population census in Norway, Tynes and Andersen (1990) identified a cohort of approximately 38 000 men aged ≥ 20 years who at that time had held jobs in which they might have been exposed to electric and magnetic fields. Cohort members were linked to the files of the Norwegian Cancer Registry and followed up for breast cancer incidence from 1961–85. A total of 12 cases of breast cancer was observed when 5.81 were expected on the basis of age- and calendar year-specific breast cancer incidence rates for all economically active men in Norway according to the census, yielding an SIR of 2.1 (95% CI, 1.1–3.6).

From the 1960 occupational cohort, a group was selected (37 945 men, aged 20–70 years) which was followed up to investigate other types of cancer in a second study (Tynes *et al*., 1992). The jobs held by cohort members were categorized into one of 12 occupational groups, each of which was classified in turn according to the anticipated type of exposure to electric and magnetic fields, i.e. (i) radiofrequency, (ii) heavy magnetic, electric, (iii) intermediate magnetic, (iv) weak magnetic, electric, and (v) weak magnetic. No supporting field measurements were made. Cohort members were linked to the files of the national Norwegian Cancer Registry and followed up for cancer incidence from 1961 until the date of death or emigration, or to the end of 1985. Overall, 3806 incident cases of cancer were observed when 3583.7 were expected on the basis of age- and calendar year-specific cancer incidence rates for all economically active men

in Norway according to the census, yielding an SIR of 1.06 (95% CI, 1.03–1.09). A total of 107 cases of leukaemia were reported, yielding a slightly increased SIR of 1.1 (95% CI, 0.9–1.3) with SIRs of 1.3 (95% CI, 0.88–1.2), 0.97 (95% CI, 0.64–1.4) and 1.5 (95% CI, 0.90–2.3) for acute myeloid, chronic lymphocytic and chronic myeloid subtypes of leukaemia, respectively. A total of 119 brain tumours were observed, which also resulted in a slightly increased SIR of 1.1 (95% CI, 0.90–1.4). In a separate analysis of the subgroup of cohort members still economically active at the time of the 1970 census, the SIR for leukaemia was 1.4 (95% CI, 1.1–1.8). On the basis of this subgroup, the authors found a tendency towards a dose–response relationship for leukaemia with SIRs of 1.8 (95% CI, 1.1–2.8), 1.4 (95% CI, 0.81–2.2) and 1.1 (95% CI, 0.70–1.6) for the exposure categories heavy magnetic, electric, intermediate magnetic and weak magnetic, respectively. No such tendency was apparent for brain tumours.

Matanoski *et al*. (1991) reported the results of a cohort study of telephone workers in the United States aged < 65 years. Central office technicians (9561), exposed to mean magnetic field strengths of 0.25 μT, had an SIR of 6.5 (95% CI, 0.79–24) for male breast cancer, based on two observed cases. These technicians were working in a central office with electromechanical switches, which produced a complex field environment. No men with breast cancer were observed among other telephone workers, in particular among cable splicers (4547) who had a mean exposure to magnetic fields of 0.43 μT. No results for leukaemia were reported in this study.

From the 1970 population census in Denmark, Guénel *et al*. (1993b) identified a total of 3932 combinations among men and 1885 combinations among women of a specific industry and a specific occupation. Only combinations in which ≥ 10 persons were involved were included. Each of these industry–occupation combinations was coded for potential occupational exposure (no exposure, probable exposure) to 50-Hz electric and magnetic fields using a threshold level of 0.3 μT, and the appropriate code was applied to the 2.8 million economically active Danes aged 20–64 years at the time of the census in 1970. Men and women judged to be occupationally exposed to intermittent magnetic fields (154 000 men, 79 000 women) and to continuous magnetic fields (18 000 men, 4000 women) were followed up in the Danish Cancer Registry until 1987. The numbers of first primary cancers observed in the exposed cohorts were compared with those expected, calculated on the basis of age-, sex- and calendar year-specific rates of primary cancer incidence among all persons who were economically active according to the census. The incidence of leukaemia was increased in men with probable continuous exposure to magnetic fields (SIR, 1.6; 95% CI, 1.2–2.2) on the basis of 39 observed cases. The excess risk was the same for acute leukaemia and for other leukaemias. The incidence of leukaemia was not increased in women with continuous exposure (SIR, 0.56; 95% CI, 0.07–2.0), but only two cases were observed. Both men and women with probable intermittent exposure to magnetic fields had leukaemia risks close to the average for all economically active persons. No significant result was found for breast cancer, brain tumours or malignant melanoma.

In a study from Sweden, Floderus *et al*. (1994) used the records from the 1960 Swedish population census to select all men, aged 20–64, who, in 1960, had been employed as workers by the Swedish railways. [The size of the cohort was not given; however, the study group appears identical to one of the 11 subcohorts included in a previous census-linkage study from Sweden (Törnqvist *et al*., 1991).] Using spot measurements, exposure to electric and magnetic fields was estimated to be of the order of 4.03–0.58 μT (engine drivers), 0.61–0.36 μT (conductors), 0.30–0.25 μT (station masters and train dispatchers) and 0.59–0.37 μT (railroad assistants and linemen). [It should be noted that the exposure assessment was made with a device having a less-than-flat frequency response (Floderus *et al*., 1993); the values quoted may therefore be underestimates.] Cohort members were linked to the national Swedish Cancer Registry and all cases of cancer notified to the cancer registry in 1961–79 were identified. All economically active men, aged 20–64 in 1960, acted as the reference population. No significantly increased relative risks were seen for leukaemia (all subtypes combined), for any of the subcohorts or for the combined cohort. In their consideration of the subtypes of leukaemia, the authors observed an increased risk for chronic lymphocytic leukaemia among engine drivers during the first decade of follow-up (1961–69) (SIR, 2.7; 95% CI, 1.0–7.4), but not in the second decade (1970–79) (SIR, 1.1; 95% CI, 0.4–2.9), but the relative risk estimates were based on only four cases of chronic lymphocytic leukaemia for each decade. No excess risks were seen for subtypes of brain tumour (astrocytoma I-II; astrocytoma III-IV) or for all subtypes combined (ICD-7 193 and astrocytoma only). But increased relative risks were observed for breast cancer, predominantly among engine drivers (SIR, 8.3; 95% CI, 2.0–34; 2 cases) and railway workers (SIR, 4.3; 95% CI, 1.6–12; 4 cases), and for tumours of the pituitary gland, predominantly among conductors (SIR, 3.3; 95% CI, 1.5–7.6; 6 cases) and railway workers (SIR, 2.9; 95% CI, 1.6–5.3; 11 cases). These results, however, were based on only a few observed cases and were seen only during the first decade of follow-up (1961–69). [The Working Group noted that calculation of person–years at risk was not corrected for elimination due to death, either in the study cohort or in the reference population. This implies that the relative risk estimates in the case of differential mortality in the study groups may have been distorted.]

In another study from Norway, Tynes *et al*. (1994a) studied the incidence of cancer in 5088 male workers in eight large hydroelectric power companies. From employment records available for each company, cohort members were selected on the following criteria: job title that indicated exposure to ELF electric and magnetic fields, employment for at least one year and first employment between 1920 and 1985. The average duration of employment among cohort members was 22 years. Spot measurements of magnetic fields were made at the two largest power companies and a job title–magnetic field exposure matrix was constructed. The matrix was applied to the work histories of the study subjects to provide calculated estimates of exposure to ELF electric and magnetic fields (μT–years) for each worker covering the period from first employment until date of retirement or the end of the study. Crude estimates of

job-related exposure to solvents, herbicides, asbestos and cable oils were also made. Cohort members were linked to the files of the national Norwegian Cancer Registry and follow-up for cancer incidence was undertaken over the period 1953–91. Overall, 486 new cases of cancer were observed which matched the number of cases expected on the basis of person–years at risk among cohort members combined with the age- and calendar year-specific cancer incidence rates of Norwegian men (SIR, 1.0; 95% CI, 0.92–1.1). No significant deviation in risk from unity was seen for cancer at any site, including leukaemia (SIR, 0.90; 95% CI, 0.45–1.6) and brain tumours (ICD-9 193) (all tumours of the central nervous system and malignant tumours of the peripheral nervous system) (SIR, 0.88; 95% CI, 0.47–1.5) with 11 and 13 observed cases, respectively. In a sub-analysis, no trends in risks for leukaemia or brain tumours with increasing time since first employment or duration of employment were observed. Also, no association with cumulative exposure to magnetic fields was seen for leukaemia while brain tumour showed a tendency towards a negative correlation. An excess risk was seen for malignant melanoma at cumulative exposures above 35 μT–years (11 cases); however, the data showed no continuous exposure–response trend.

A mortality study was conducted in a cohort of workers at five electric utility companies in the USA (Savitz & Loomis, 1995). All men employed full-time continuously for at least six months between 1950 and 1986 were included. Vital status until 31 December 1988 was ascertained leading to the identification of 20 733 workers who had died out of a total of 138 905 workers. Exposure to magnetic fields was estimated from a job–exposure matrix, elaborated from exposure measurements made on workers randomly selected within occupational groups in each company. These measurements were taken using the AMEX meter which yields a TWA exposure. In total, 2842 usable measurements of a one-day work shift were collected. These were aggregated in five occupational groups to obtain maximum internal precision of the mean magnetic field within a group and maximum variability of mean magnetic field between groups. Occupational exposure to solvents and polychlorinated biphenyls was estimated for each occupational category through expert judgement. In the initial study, these analyses were restricted to total mortality (20 733 cases), total cancer (4833 cases), leukaemia (164 cases) and brain cancers (ICD-9 191, 192) (144 cases). A slight increased risk for brain cancer was apparent for workers employed in highly exposed occupations. The risk for leukaemia was increased for workers who had been employed for 20 years or more as electricians: SMR, 2.5 (95% CI, 1.1–5.8; 6 cases), but not in other exposed occupations. The risk for total cancer was slightly increased with indices of exposure to magnetic fields. Brain cancer, but not leukaemia, was associated with total exposure to magnetic fields, with a relative risk adjusted for potential occupational confounders of 2.3 (95% CI, 1.2–4.6) in the highest exposure category (≥ 4.3 μT–years, 90th percentile). The association with brain cancer was more apparent for recent exposure to magnetic fields, i.e. for exposure in the interval 2–10 years before death, suggesting a relatively short latency period: SMR, 1.2 (95% CI, 0.66–2.1), 1.4 (95% CI, 0.75–2.6), 1.5 (95% CI, 0.76–2.8) and 2.6 (95% CI, 1.4–4.9) for 0–< 0.2, 0.2–< 0.4;

0.4–< 0.7 and ≥ 0.7 μT–years, respectively. The relationship of brain cancer mortality to cumulative exposure to magnetic fields was not sensitive to the method used to treat historical exposure, the choice of exposure-time lags and windows, and the cut-points used to categorize the exposure variables (Loomis *et al*., 1998). Using a case–cohort approach and a refined job–exposure matrix with more precise job definitions, Savitz *et al*. (2000) found that the rate ratios for brain cancer were essentially unchanged; a weak positive association with leukaemia was apparent. Mortality from non-Hodgkin lymphoma, Hodgkin disease and multiple myeloma in this cohort were investigated by Schroeder and Savitz (1997). Weak associations between total exposure to magnetic fields and non-Hodgkin lymphoma were observed at intermediate exposure levels, with a weaker association in the highest exposure category. No association was observed with Hodgkin disease or multiple myeloma.

Mortality from lung cancer in this cohort in relation to magnetic fields has also been reported (Savitz *et al*., 1997). The rate ratio for lung cancer in the highest category of cumulative exposure to magnetic fields (4.28–15.45 μT–years, 90th percentile) was 1.1 (95% CI, 0.89–1.3). Modest associations were observed with exposure estimated in several time windows before death, or for duration of employment over 20 years in specific occupational groups exposed to strong 60-Hz magnetic fields, such as electricians or power plant operators. [The Working Group noted that adjustment for tobacco smoking was not feasible.]

In another study from Sweden, Alfredsson *et al.* (1996) investigated the incidence of cancer in 7466 railway engine drivers and 2272 conductors, who were employed by the Swedish State Railways on 1 January 1976 or who had started their employment there at any time during the period 1976–90. Information on date of hire, date of leaving and type of job was obtained from registers kept by the State Railways. No measurements of exposure to magnetic fields were made. Cohort members were followed up for cancer in the Swedish National Cancer Registry from date of first hire or 1 January 1976, whichever came first, until date of death or diagnosis, or until the end of 1990. The observed numbers of cohort members diagnosed with a first primary cancer were compared with the expected numbers calculated on the basis of person–years of follow-up among cohort members and cancer incidence rates of the general male population of Sweden. A total of 630 workers with cancers at all sites combined was observed (486 among railway engine drivers and 144 among conductors) yielding a relative risk of 0.9 (95% CI, 0.8–1.0). For railway engine drivers and conductors combined, the relative risk for acute lymphoblastic or chronic lymphocytic leukaemia was 1.6 (95% CI, 0.9–2.6). In a supplementary analysis where follow-up was restricted to workers in the age range 20–64 years, the authors found that the relative risk estimate was further increased: 2.3 (95% CI, 1.3–3.2). No clear association was seen for the other subtypes of leukaemia. For astrocytoma, the relative risk was close to one. [The Working Group noted that there must have been a substantial overlap between this study population and that studied by Floderus *et al.* (1994). It was not clear whether

cancer reference rates including multiple cancers in individuals were used for the calculation of the expected numbers of cancers.]

Johansen and Olsen (1998) evaluated the incidence of cancer in a study population composed of 32 006 men and women with at least three months of employment at the 99 utility companies that supply Denmark with electricity. Personal data were obtained from manual files kept by the electricity companies, the Danish Supplementary Pension Fund and the public payroll administration; the date of first employment ranged from 1908–93. On the basis of a series of 24-h personal measurements and the judgements of four engineers, each of a total of 475 combinations of job title and work area for employees were assigned an average level of exposure to ELF electric and magnetic fields during a working day. These were in turn grouped into one of five categories according to exposure level: background (< 0.09 μT), low (0.1–0.29 μT), medium (0.3–0.99 μT), high (> 1.0 μT) and unknown exposure. A rough estimate was also made of exposure to asbestos. Cohort members were linked to the files of the national Danish Cancer Registry and follow-up for cancer was from 1968 until date of death, date of emigration or the end of 1993. Overall, 3008 cohort members with cancer were observed, as against 2825 expected on the basis of person–years at risk among cohort members combined with age-, sex- and calendar year-specific cancer incidence rates for the Danish population, yielding an SIR of 1.06 (95% CI, 1.03–1.10). No excess risk was seen for leukaemia [SIR, 0.88] or tumours of the brain [SIR, 0.86]; the overall reduction in the relative risk for brain tumours was due to a reduced risk of borderline significance (SIR, 0.79; 95% CI, 0.6–1.0) in men. Similarly, no excess was seen for any of the major subtypes of leukaemia, and no trends in risk could be distinguished for leukaemia or tumours of the brain in relation to time since first employment. Finally, there was no indication of a link between cumulative exposure to ELF electric and magnetic fields (duration of work combined with level of exposure) and the risk for any of these tumour types. Only two cases of breast cancer were seen in men, as against four expected, while the relative risk for breast cancer in female employees was slightly elevated (SIR, 1.1; 95% CI, 0.9–1.3), but breast cancer in women showed no correlation with cumulative exposure to ELF electric and magnetic fields. Increased risks for cancers of the lung and pleural cavity were seen mainly in workers whose jobs involved exposure to asbestos.

Petralia *et al*. (1998) carried out a study in urban Shanghai, the People's Republic of China, where all incident cases of breast cancer in women ≥ 30 years old in 1980–84 were identified. The incidence rates of breast cancer were calculated using the 1982 census data for the same population and SIRs were calculated with these rates as a reference. The extent of exposure to electric and magnetic fields was estimated through a job–exposure matrix using scores for exposure probability (high, medium, low or none) and exposure levels (high, medium, low or none). Using the occupation at the time of diagnosis for classifying women into exposure groups, electric and magnetic fields were not found to be related to breast cancer incidence; SIRs were close to 1.0 in all exposure categories for any exposure index.

In a linkage study from Sweden, Floderus *et al*. (1999) used data from the 1970 population census to evaluate overall and site-specific cancer incidence among 1 596 959 men and 806 278 women, aged 20–64 years in 1970, who had all been employed in a job the title of which had been included in a previously established job–exposure matrix for ELF electric and magnetic fields. This job–exposure matrix gave estimates of magnetic field exposure for the 100 most common jobs in Sweden according to the 1990 census, and for 10 specifically selected occupations that were less common, but more heavily exposed to ELF electric and magnetic fields (Floderus *et al*., 1993, 1996). This job–exposure matrix formed the basis for allocation of levels of exposure to magnetic fields to the jobs included in the study. Cohort members were linked to the files of the national Swedish Cancer Registry and followed up for cancer incidence from 1971 through 1984; follow-up was discontinued when members reached 70 years of age. Cumulative incidence rates, adjusted for age, but unadjusted for mortality during follow up, were calculated for all men and women employed in jobs categorized as having medium exposure (men, 0.084–0.115 μT; women, 0.067–0.129 μT) and high exposure (men, ≥ 0.116 μT; women, ≥ 0.138 μT) [and presumably compared with those of all men and women included in the study]. The risk ratios for cancer at all sites combined in the investigators' medium and high exposure categories, respectively, were 1.1 (95% CI, 1.1–1.1) and 1.1 (95% CI, 1.1–1.1) for men, and 1.1 (95% CI, 1.0–1.1) and 1.1 (95% CI, 1.0–1.1) for women. Similar results were seen for brain tumours (nervous system) and leukaemia with risk ratios of 1.1 (95% CI, 1.0–1.2) and 1.1 (95% CI, 1.0–1.2), respectively, in the highest exposure tertile for men and 0.9 (95% CI, 0.8–1.1) and 1.1 (95% CI, 1.0–1.4) for women. Also, in the highest tertile, male breast cancer was non-significantly increased (risk ratio, 1.2; 95% CI, 0.7–1.9). The risk ratios for cancer at several other sites were slightly increased in the upper exposure tertile, including malignant melanoma among men (risk ratio, 1.4; 95% CI, 1.2–1.5) and women (risk ratio, 1.2; 95% CI, 1.1–1.4); however, there was no general exposure–response pattern. [The Working Group noted that the study population must be partly overlapping with that included in a previous Swedish study by Törnqvist *et al*. (1991). The Working Group also noted that no measurements of cumulative exposure to magnetic fields were available, introducing a high risk for misclassification of the exposure of study subjects, and that no adjustment was made in the risk ratio analysis for mortality among study subjects during follow-up.]

In a linkage study from Norway, Kliukiene *et al*. (1999) used data from the 1960, 1970 and 1980 population censuses to evaluate the incidence of breast cancer in 1 177 129 women who were economically active according to at least one of the censuses. The classification of a job was based on a 3–5-digit industry code and a 3-digit occupation code; the socioeconomic status of the women was defined according to the job title. For a subcohort of women born in 1935 or later, data on age at birth of first child were also available. Exposure to ELF magnetic fields was assessed *a priori* using two different approaches. In the first approach, the number of hours per week during which potential magnetic fields were estimated to be above a background level, defined

as 0.1 μT, were classified by an expert panel. In the second approach, measurements of magnetic fields from a previous study (Floderus *et al.*, 1996) of Swedish men were allocated to the women's job titles as reported in the census. In both approaches, exposure was cumulated over years of employment (work hours and μT–years, respectively). Cohort members were linked to the National Cancer Registry for identification of notified cases of breast cancer, and person–years at risk were calculated from the year of entering the study to the date of death or emigration, or to the end of 1992. The SIRs for breast cancer among cohort members were calculated using the rates for the total Norwegian population as a reference. In the two highest categories for number of work hours with exposure to ELF magnetic fields above background, i.e. 1000–1999 h and ≥ 2000 h, the SIRs were 1.05 (95% CI, 1.02–1.07) and 1.08 (95% CI, 1.05–1.12), respectively. The SIRs in the two upper categories for cumulative exposure in μT–years, i.e. 1.5–3.0 and > 3.0 were 1.06 (95% CI, 1.03–1.09) and 1.03 (95% CI, 0.97–1.09), respectively. Using the lowest exposure category as a reference (0 h exposure above background, and cumulative exposure between 0.1 and 0.8 μT–years) and adjusting for socioeconomic status (based on the job title) a Poisson regression analysis showed a risk ratio for breast cancer for the two highest categories for number of work hours with exposure to magnetic fields above background, of 1.08 (95% CI, 1.04–1.12) and 1.14 (95% CI, 1.10–1.19), respectively, and for the highest categories of cumulative exposure of 1.12 (95% CI, 1.07–1.17) and 1.08 (95% CI, 1.01–1.16), respectively. In the subcohort of women born in 1935 or later, the corresponding risk ratio was somewhat lower, and of marginal significance, after adjustment for age at birth of first child.

From employment records, Pira *et al.* (1999) identified a total of 4237 subjects who had worked for at least three months in a geothermal power plant in Italy between 1950 and 1990. After exclusion of all the 225 female workers of 36 men who could not be traced, the remaining 3946 male workers were traced for date of death and cause of death, whenever appropriate, from death certificates and from population files kept by the local municipality. A total of 977 deaths was registered as opposed to 1295 expected on the basis of age- and calendar year-specific national mortality rates applied to the person–years at risk among cohort members, yielding a SMR of 0.75 (95% CI, 0.71–0.80). Eight of the deaths were due to leukaemia and 11 to tumours of the brain and nervous system yielding SMRs of 0.79 (95% CI, 0.34–1.6) and 1.2 (95% CI, 0.57–2.1), respectively. The authors reviewed the working histories of these patients at the power plant and stated that none had worked in activities for which exposure to electric and magnetic fields could be presumed to have occurred.

Mortality from leukaemia was investigated by Harrington *et al.* (2001) in a cohort of 83 977 male and female electricity generation and transmission workers at the former Central Electricity Generating Board of England and Wales for whom computer records were available. All employees were known to have been employed for at least six months with some period of employment in the period 1973–82. Work history records were available until 1993. On the basis of the results from a previous measurement programme on occupational exposure to ELF electric and magnetic fields in parts of the

United Kingdom, exposure of workers in the electricity generation and transmission industry was estimated for 11 different work categories for power-station workers and eight categories for transmission workers. The job history for each worker was classified according to the established job categories and the cumulative occupational lifetime exposure (level multiplied by duration; μT–years) was estimated for each individual. The cumulative exposure in the most recent five-year period was also estimated. The mortality of the total cohort until 1997 was obtained by record linkage with the mortality files of the Central Register of the National Health Service. Compared with mortality rates from England and Wales, the overall SMR from leukaemia among cohort members was 0.84 (95% CI, 0.69–1.01) on the basis of 111 observed cases. Subanalyses by period from date of hire or according to subtype of leukaemia showed no consistent pattern. In the subcohort of 79 972 workers for whom work history data were available, a Poisson regression analysis showed age- and sex-adjusted relative risks of death from leukaemia of 1.5 (95% CI, 0.87–2.5), 0.99 (95% CI, 0.59–1.7), 0.96 (95% CI, 0.55–1.7) and 1.4 (95% CI, 0.68–2.8) among cohort members with a lifetime exposure of 2.5–4.9, 5.0–9.9, 10.0–19.9 and ≥ 20.0 μT–years, respectively, compared with the risk of death from leukaemia among workers with cumulative exposures ≤ 2.4 μT–years. Dose analyses on subtypes showed that only one point estimate, i.e. 'other leukaemias' in the lowest category of exposure, was significantly different from unity (relative risk, 2.0; 95% CI, 1.1–3.7). There was no significant trend of risk for any subtype of leukaemia or for all leukaemias combined with increasing cumulative exposure. A re-analysis using the most recent five years of exposure to ELF electric and magnetic fields did not change the results.

A retrospective cohort mortality study of Swiss Railway employees occupationally exposed to magnetic fields of 16 2/3-Hz and substantial harmonics was conducted by Minder and Pfluger (2001). The cohort comprised all men actively employed as line engineers, shunting-yard engineers, train attendants or stationmasters, or retired from these jobs and alive, identified through several personnel and pension records starting in 1972. The total number of men in the cohort was 18 070, representing 270 155 person–years of observation from 1972–93. Deaths of cohort members from leukaemia or brain tumour identified from death certificates were used as end-points. The assessment of exposure was carried out using a device that measured the magnetic fields in the driver's seat of the engine during complete driving cycles, for different types of train and routes taken. Historical exposure for each five-year calendar period was also assessed based on the number of engines in service and a weighted average of engine-specific exposure. The exposure to magnetic fields of train attendants and stationmasters was assessed from measurements taken at their most frequent places of work. Each cohort member was assigned the exposure associated with his last reported job, which was also generally of the longest duration, due to infrequent job changes. Estimated cumulative exposure in μT–years increased in the period 1930–90 from 9.3 to 25.9 for line engineers, from 2.6 to 13.4 for shunting-yard engineers, from 0.4 to 3.3 for train attendants and from 0.1 to 1.0 for stationmasters. When compared with stationmasters

with the lowest exposure, the relative risk for leukaemia was 2.4 (95% CI, 0.97–6.1) for line engineers and 2.0 (95% CI, 0.50–8.1) for shunting-yard engineers. The relative risk for brain tumours (ICD-9 191) was 1.0 (95% CI, 0.23–4.6) for line engineers and 5.1 (95% CI, 1.2–21) for shunting-yard engineers. For cumulative exposure ≥ 75 μT–years compared with exposure 0–4.9 μT–years, the relative risk was 1.6 (95% CI, 0.64–4.2) for leukaemia and 2.4 (95% CI, 0.29–19) for brain tumours. The trend of increasing leukaemia mortality with both cumulative exposure and fraction of time above 10 μT was statistically significant.

(*c*) *Case–control studies*

In the first published studies on occupational exposure to electric and magnetic fields, no measurements of exposure were made; exposure was inferred from the job title, on the assumption that electrical workers were exposed to higher than background fields. Job–exposure matrices, which included scores for exposure probability and exposure intensity in exposed occupations as determined from expert judgement, have also been used. In most studies, no data on exposure to other potential carcinogens were available. Some of the studies presented as case–control studies are based on mortality data collected from death certificates. In these studies, the 'cases' were deaths from the cause of interest (i.e. leukaemia, brain tumour or breast cancer) and the controls were selected from other causes of death; such studies should be seen as mainly exploratory.

More recent studies have included exposure measurements and concerned mostly occupational cohorts analysed using a nested case–control study design. In some instances, the results have been presented according to the type of field measured (i.e. ELF magnetic fields, ELF electric fields). Exposure to potential occupational confounders was generally assessed in these studies.

The results of the case–control studies of ELF magnetic fields are summarized in Table 30 and for ELF electric fields in Table 31.

(i) *Leukaemia*

In a case–control study, McDowall (1983) used the deaths recorded in England and Wales for the year 1973. The cases selected were 537 men who had died aged ≥ 15 years from acute myeloid leukaemia. A total of 1074 controls were randomly selected from men who had died aged ≥ 15 years from all causes except leukaemia to match the cases within five-year age groups. The analysis showed an increased odds ratio for acute myeloid leukaemia for all five of the electrical occupations studied; however, this was statistically significant only when all five occupations were analysed combined (odds ratio, 2.1; 95% CI, 1.3–3.6). Further evaluation of the group of 'all electrical occupations and persons of any occupation engaged in an electrical telecommunications industry' gave an odds ratio of 2.3 (95% CI, 1.4–3.7).

In a population-based case–control study, Pearce *et al*. (1985) identified 546 cases of leukaemia among men aged ≥ 20 years notified to the cancer registry of New Zealand during 1979–83. The 2184 controls were men chosen at random from the

Table 30. Case–control studies of occupational groups with assumed or documented exposure to ELF magnetic fields

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
Leukaemia								
England and Wales (McDowall, 1983)	537 male deaths from AML 1074 male deaths from other causes (controls) (1973)	Death certificates	Death certificates; occupation	All electrical occupations Any occupation in electrical or telecommunications industry	30 36	2.1 2.3	(1.3–3.6) (1.4–3.7)	Matched on age
New Zealand (Pearce *et al*., 1985)	546 men with leukaemia 2184 men with other cancers (controls) (1979–83)	Cancer registry	Cancer registry; occupation	All electrical occupations	18	1.7	(0.97–3.0)	Matched on age
New Zealand (Pearce *et al*., 1989) [partly overlapping with Pearce *et al*. (1985)]	534 men with leukaemia 19 370 men with other cancers (controls) (1980–84)	Cancer registry	Cancer registry; occupation	All electrical work age 20–64 age ≥ 65	21 9 12	1.6 1.4 1.9	(1.0–2.5) (0.71–2.7) (1.0–3.3)	
	Chronic leukaemia Acute leukaemia				11 6	2.1 1.3	(1.2–3.8) (0.62–2.5)	
USA (Loomis & Savitz, 1990)	3400 male deaths from leukaemia 34 000 male deaths from other causes (controls) (1985–86)	Death certificates; 16 states in the USA	Death certificates	Electrical occupations	76	1.0	(0.8–1.2)	Adjusted for race and age
	903 deaths from AML				22	1.1	(0.7–1.7)	Not adjusted
	414 deaths from CNLL				11	1.1	(0.8–1.7)	Not adjusted
	181 deaths from ALL				6	1.5	(0.7–3.4)	Not adjusted
	800 deaths from CLL				11	0.6	(0.3–1.1)	Not adjusted

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields		No. of cases	Odds ratio (95% CI)		Comments
France (Richardson *et al*., 1992)	185 men and women with acute leukaemia 513 men and women with other diseases (controls) (1984–88)	In-patient files; two hospitals	Interview; job–exposure assessment	Any exposure		14	1.7	(0.9–3.5)	Matched on sex, age, ethnic group and place of residence
				Other than from arc welding					Adjusted for prior chemo-therapy or radiotherapy
				Any		7	3.9	(1.2–13)	
				Moderate/higher		3	2.9	(0.6–14)	
Italy (Ciccone *et al*., 1993)	86 men and women with myeloid leukaemia or MDS 246 hospital and population controls (1989–90)	In-patient files	Personal interview; job–exposure matrix	**Possibly and probably exposed**					Matched on sex, age and area of residence
				Men		17	1.6	(0.6–4.1)	
				Women		4	0.8	(0.2–2.5)	
USA (Sahl *et al*.,1993; Kheifets *et al*., 1999)	44 deaths from leukaemia 438 cohort controls (1960–88)	Cohort of electric utility workers	Company personnel records; job–exposure matrix based on measured magnetic fields	< 4 μT–years		6	1.0	(baseline)	
				4–8 μT–years		3	1.0	(0.2–4.8)	
				8–16 μT–years		7	1.6	(0.4–6.4)	
				>16 μT–years		15	1.5	(0.4–6.3)	
Sweden (Floderus *et al*., 1993)	250 men with leukaemia 1121 male population controls (1983–87)	Cancer registry; population registry	Mailed question-naire and spot measurements; job–exposure matrix	**Mean level**					Matched on age
				≤ 0.15 μT	(Q1)	48	1.0	(baseline)	
				0.16–0.19 μT	(Q2)	50	0.9	(0.6–1.4)	
				0.20–0.28 μT	(Q3)	61	1.2	(0.8–1.9)	
				≥ 0.29 μT	(Q4)	80	1.6	(1.1–2.4)	
				≥ 0.41 μT	(90%)	32	1.7	(1.0–2.7)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields		No. of cases	Odds ratio (95% CI)		Comments
	112 men with CLL			≤ 0.15 μT	(Q1)	13	1.0	(baseline)	
				0.16–0.19 μT	(Q2)	17	1.1	(0.5–2.3)	
				0.20–0.28 μT	(Q3)	33	2.2	(1.1–4.3)	
				≥ 0.29 μT	(Q4)	41	3.0	(1.6–5.8)	
				≥ 0.41 μT	(90%)	22	3.7	(1.8–7.7)	
	90 men with AML			≤ 0.15 μT	(Q1)	22	1.0	(baseline)	
				0.16–0.19 μT	(Q2)	24	1.0	(0.5–1.8)	
				0.20–0.28 μT	(Q3)	18	0.8	(0.4–1.6)	
				≥ 0.29 μT	(Q4)	23	1.0	(0.6–1.9)	
				≥ 0.41 μT	(90%)	8	0.9	(0.4–2.1)	
USA (London *et al*., 1994)	2355 men with leukaemia 67 212 men with other cancers (controls) (1972–90)	Los Angeles county cancer registry	Job at diagnosis from medical record; job–exposure matrix based on measured magnetic fields in selected occupations	**Average level**					
				< 0.17 μT		2264	1.0	(baseline)	
				0.18–0.80 μT		61	1.2	(1.0–1.6)	
				≥ 0.81 μT		30	1.4	(1.0–2.0)	
	853 men with ANLL			< 0.17 μT		820	1.0	(baseline)	
				0.18–0.80 μT		23	1.3	(0.9–1.9)	
				≥ 0.81 μT		10	1.3	(0.7–2.3)	
	534 men with CLL			< 0.17 μT		512	1.0	(baseline)	
				0.18–0.80 μT		18	1.6	(1.2–2.3)	
				≥ 0.81 μT		4	0.8	(0.4–1.5)	
	487 men with CML			< 0.17 μT		469	1.0	(baseline)	
				0.18–0.80 μT		8	0.8	(0.5–1.3)	
				≥ 0.81 μT		10	2.3	(1.4–3.8)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
Norway (Tynes *et al*., 1994a)	52 men with leukaemia 259 cohort controls (1958–90)	Cohort of railway workers	Job history from employment files; job–exposure matrix	Ever worked at an electric line	33	0.7	(0.37–1.4)	Matched on age
				Cumulative exposure				
				None	19	1.0	(baseline)	
				Low (0.1–310 μT–years)	22	1.0	(0.49–2.1)	
				High (311–3600 μT–years)	11	0.49	(0.22–1.1)	
				Very high (1900–3600 μT–years)	4	0.84	(0.25–2.8)	
Canada, France (3 cohorts combined) (Thériault *et al*., 1994)	140 incident cases of leukaemia 546 cohort controls (Canada, 1970–88; France, 1978–89)	Three cohorts of electric utility workers in Canada (Quebec and Ontario) and France	Company personnel records; job–exposure matrix based on measurements of exposure to magnetic fields	**Cumulative exposure**				
				< 3.1 μT–years	70	1.0	(baseline)	
				> 3.1 μT–years	70	1.5	(0.90–2.6)	
				> 15.7 μT–years	13	1.8	(0.77–4.0)	
	60 incident cases of ANLL 238 cohort controls			< 3.1 μT–years	27	1.0	(baseline)	
				> 3.1 μT–years	33	2.4	(1.1–5.4)	
				> 15.7 μT–years	6	2.5	(0.70–9.1)	
	24 incident cases of CML 93 cohort controls			< 3.1 μT–years	16	1.0	(baseline)	
				> 3.1 μT–years	8	0.61	(0.18–2.1)	
	14 incident cases of ALL 55 cohort controls			< 3.1 μT–years	10	1.0	(baseline)	
				> 3.1 μT–years	4	2.1	(0.12–35)	
	41 incident cases of CLL 157 cohort controls			< 3.1 μT–years	17	1.0	(baseline)	
				> 3.1 μT–years	24	1.5	(0.50–4.4)	
				> 15.7 μT–years	6	1.7	(0.44–6.7)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
Quebec cohort (included in Thériault *et al.*, 1994)	24 men with leukaemia 95 cohort controls (1970–88)			**Cumulative exposure** < 3.1 μT–years > 3.1 μT–years > 15.7 μT–years	 6 18 4	 1.0 0.29 0.45	 (baseline) (0.04–1.8) (0.04–3.8)	
	[8 men with ANLL] 32 cohort controls			< 3.1 μT–years > 3.1 μT–years >15.7 μT–years	1 [7] 2	1.0 0.75 0.14	(baseline) (0.00–> 100) (0.00–> 100)	
	10 men with CLL 40 cohort controls			< 3.1 μT–years > 3.1 μT–years >15.7 μT–years	3 7 2	1.0 0.25 0.27	(baseline) (0.02–2.6) (0.02–4.2)	
France cohort (included in Thériault *et al.*, 1994)	71 incident cases of leukaemia 279 cohort controls (1978–89)			**Cumulative exposure** < 3.1 μT–years > 3.1 μT–years > 15.7 μT–years	 55 16 3	 1.0 1.4 1.9	 (baseline) (0.61–3.1) (0.46–7.8)	
	34 men with ANLL 134 cohort controls			< 3.1 μT–years > 3.1 μT–years > 15.7 μT–years	24 10 1	1.0 1.8 1.4	(baseline) (0.57–5.4) (0.03–16.2)	
	13 men with CLL 51 cohort controls			< 3.1 μT–years > 3.1 μT–years > 15.7 μT–years	10 3 1	1.0 4.8 2.8	(baseline) (0.45–71) (0.04–68)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
Canada, Ontario cohort included in Thériault *et al.*, 1994), updated Miller *et al*. (1996)[a]	50 men with leukaemia 199 cohort controls 1970–88	Cohort of electric utility workers at Ontario Hydro	Company personnel records; job–exposure matrix for magnetic fields (Positron meter)	**Cumulative exposure** < 3.1 μT–years 3.2–7 μT–years ≥ 7.1 μT–years	 10 16 24	 1.0 1.7 1.6	 (baseline) (0.58–4.8) (0.47–5.1)	Adjustment for potential confounders
	20 men with ANLL [80 cohort controls]			< 3.1 μT–years 3.2–7 μT–years ≥ 7.1 μT–years	3 6 11	1.0 1.9 2.9	(baseline) (0.27–14) (0.42–20)	
	19 men with CLL [76 cohort controls]			< 3.1 μT–years 3.2–7 μT–years ≥ 7.1 μT–years	4 6 9	1.0 0.49 0.25	(baseline) (0.06–4.2) (0.01–4.6)	
Brain tumours								
USA (Lin *et al*., 1985)	519 male deaths from brain tumours (370 gliomas or glioblastoma multiforme, and 149 astrocytomas) 519 male deaths from other causes (controls)	Maryland state vital records	Job on death certificate; job–exposure matrix	No exposure Possible exposure Probable exposure Definite exposure	323 128 21 27	1.0 1.4 2.0 2.2	 (1.1–2.0) (0.94–3.9) (1.1–4.1)	
	432 male deaths from brain tumours of unspecified type 432 male deaths from other causes (controls) (1969–82)			No exposure Possible exposure Probable exposure Definite exposure	286 87 19 15	1.0 0.94 1.3 1.5	 (0.68–1.3) (0.60–2.8) (0.68–3.4)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
USA (Speers *et al*., 1988)	202 male deaths from glioma 238 male deaths from other causes (controls) (1969–78)	Death certificates (East Texas)	Job on death certificate; job–exposure matrix	No exposure Possible exposure Probable exposure Definite exposure	92 68 11 6	1.0 1.2 2.9 infinite	 (0.73–1.8) 0.80–10) $p = 0.009$	Adjusted for age
New Zealand (Pearce *et al*., 1989)	431 men with malignant brain tumours (ICD-9 191) 19 473 men with other cancers (controls) (1980–84)	Cancer registry	Cancer registry occupation	All electrical workers	12	1.0	(0.56–1.8)	
USA (Preston-Martin *et al*., 1989)	202 men with glioma 202 male neighbourhood controls (1980–84)	Los Angeles County Cancer Registry	Work history from questionnaire; electrical occupations	Any exposure duration < 5 years > 5 years	14/8 16 14	1.8 1.4 1.8	(0.7–4.8) (0.7–3.1) (0.8–4.3)	No. of discordant pairs
	70 men with meningioma 70 neighbourhood controls			Any exposure duration	2/3	0.7	(0.1–5.8)	No. of discordant pairs
USA (Loomis & Savitz, 1990)	2173 male deaths from brain cancer (ICD-9 191) 21 730 male deaths from other causes (1985–86)	Death certificates (16 US states)	Death certificate; occupation	Electrical occupations	75	1.4	(1.1–1.7)	Adjusted for race and age

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
Australia (Ryan *et al.*, 1992)	110 glioma 60 meningioma 417 controls (1987–90)					0.75 0.90	(0.30–1.9) (0.20–4.1)	
Sweden (Floderus *et al*., 1993)	261 men with brain tumours (astrocytomas and oligodendrogliomas) 1121 male population controls (1983–87)	Cancer registry/ population registry	Postal question-naire and spot measurements; job–exposure matrix	**Mean level** ≤ 0.15 µT (Q1) 0.16–0.19 µT (Q2) 0.20–0.28 µT (Q3) ≥ 0.29 µT (Q4) ≥ 0.41 µT	 53 59 72 74 24	 1.0 1.0 1.5 1.4 1.2	 (baseline) (0.7–1.6) (1.0–2.2) (0.9–2.1) (0.7–2.1)	Matched on age
USA (Sahl *et al*.,1993)	31 deaths from brain cancer (ICD-9 191) 286 cohort controls	Cohort of electric utility workers	Company personnel records; job–exposure matrix based on measured magnetic fields	Treating cumulative mean exposure as a continuous variable. Odds ratio per 25 µT–years of exposure	4	0.81	(0.48–1.4)	
Canada, France (3 cohorts combined) (Thériault *et al*., 1994)	108 men with brain cancer (ICD-9 191) 415 cohort controls	Three cohorts of electric utility workers in Canada (Québec and Ontario) and France	Company personnel records; job–exposure matrix based on measurements of exposure to magnetic fields (Positron meter)	**Cumulative exposure** < 3.1 µT–years > 3.1 µT–years > 15.7 µT–years	 60 48 12	 1.0 1.5 2.0	 (baseline) (0.85–2.8) (0.76–5.0)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
Quebec cohort (Thériault *et al*., 1994)	24 men with brain cancer 94 cohort controls (1970–88)			**Cumulative exposure** < 3.1 μT–years > 3.1 μT–years > 15.7 μT–years	 6 18 6	 1.0 1.6 1.7	 (baseline) (0.38–6.8) (0.29–9.7)	
Ontario cohort (Thériault *et al*., 1994)	24 men with brain cancer 90 cohort controls (1970–88)			**Cumulative exposure** < 3.1 μT–years > 3.1 μT–years > 15.7 μT–years	 7 17 4	 1.0 1.9 5.5	 (baseline) (0.53–6.5) (0.59–51)	
France cohort (Thériault *et al*., 1994)	60 men with brain cancer 231 cohort controls (1978–89)			**Cumulative exposure** < 3.1 μT–years >3.1 μT–years >15.7 μT–years	 47 13 2	 1.0 1.4 NR	 (baseline) (0.65–3.1) –	
Norway (Tynes *et al*., 1994a)	39 men with brain tumours 194 cohort controls (1958–90)	Cohort of railway workers	Job history from employment files; job–exposure matrix	Ever worked at an electric line **Cumulative exposure** None Low (0.1–310 μT–years) High (311–3600 μT–years) Very high (1900–3600 μT–years)	28 11 14 14 3	0.82 1.0 0.81 0.94 0.97	(0.38–1.8) (baseline) (0.33–2.0) (0.39–2.3) (0.24–4.0)	Matched on age Unadjusted
USA (Grayson, 1996)	230 men with brain cancer (ICD-9 191) 920 cohort controls (1970–89)	Cohort of male members of the US Air Force	Work history from personnel records; job–exposure matrix (scores for exposure probability)	Ever exposed 1–59[b] 60–134 135–270 271–885	129 39 33 44 13	1.3 1.3 0.93 1.6 1.4	(0.95–1.7) (0.81–2.1) (0.56–1.5) (1.0–2.6) (0.88–2.3)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
England & Wales (Harrington *et al*., 1997)	112 men and women with brain cancer (primary) 654 cohort controls (1972–84)	Cohort of electricity generation and transmission workers	Job history from employment files; job–exposure matrix	≤ 3.0 μT–years 3.1–5.9 μT–years ≥ 6.0 μT–years Unclassifiable	30 37 27 18	1.0 1.3 0.91 1.8	(baseline) (0.75–2.2) (0.51–1.6) (0.93–3.6)	
Sweden (Rodvall *et al*., 1998)	84 men with glioma 155 population controls (1987–90)	In-patient files and cancer registry/ population registry	Postal question-naire; job–exposure matrix	< 0.20 μT > 0.40 μT		1.0 1.9	(baseline) (0.8–5.0)	Adjusted for socio-economic status and exposure to solvents and plastic materials
	20 men with meningioma 155 population controls			< 0.20 μT > 0.40 μT		1.0 1.6	(baseline) (0.3-10)	
USA (Cocco *et al*., 1998a)	28 416 deaths from central nervous system cancer (men and women) 113 664 deaths from other causes (controls) (1984–92)	Death certificates (24 US states)	Job on death certificate; job–exposure matrix (exposure yes/no)	White men Black men White women Black women	5271 234 1382 78	1.0 1.0 1.0 1.2	(1.0–1.0) (0.8–1.2) (0.9–1.1) (0.9–1.6)	Adjusted for socioeconomic status and other variables
USA (Cocco *et al*., 1999)	12 980 female deaths from central nervous system cancer + meningioma 51 920 deaths from other causes (controls) (1984–92)	Death certificates (24 US states)	Job on death certificate; job–exposure matrix: probability and intensity of exposure					

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
	12 819 deaths from central nervous system cancer			Any exposure level	2901	1.2	(1.1–1.2)	
				Probability				
				Low	2312	1.2	(1.1–1.2)	
				Medium	255	1.2	(1.0–1.4)	
				High	334	1.2	(1.0–1.3)	
				Intensity				
				Low	2200	1.2	(1.1–1.2)	
				Medium	616	1.1	(1.0–1.3)	
				High	85	1.3	(1.0–1.6)	
	161 deaths from meningioma			Any exposure level	34	0.9	(0.6–1.4)	
Breast cancer								
Women								
USA (Loomis *et al*., 1994b) [included in Cantor *et al*., 1995]	28 434 deaths from breast cancer (women, excluding homemakers) 113 011 other causes of death (controls) (1985–89)	Death certificates (24 US states)	Job on death certificate; occupation	Electrical occupations	68	1.4	(1.0–1.8)	Adjusted for age, race, social class
USA (Cantor *et al*., 1995)	33 509 deaths from breast cancer (women, excluding homemakers) 117 794 other causes of death (controls) (1984–89)		Job on death certificate; job–exposure matrix: probability and level of exposure	*White women*				
				Probability				
				Low	8581	0.92	(0.89–0.95)	
				Medium	779	1.1	(1.05–1.3)	
				High	1869	1.1	(1.02–1.2)	
				Level				
				Low	9360	0.94	(0.9–0.96)	
				Medium	1746	1.1	(1.03–1.2)	
				High	123	0.97	(0.8–1.2)	

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
				Black women				
				Probability				
				Low	1516	0.81	(0.7–0.9)	
				Medium	168	1.3	(1.1–1.6)	
				High	293	1.3	(1.1–1.6)	
				Level				
				Low	1684	0.85	(0.8–0.92)	
				Medium	273	1.3	(1.1–1.5)	
				High	20	1.2	(0.7–2.1)	
USA (Coogan *et al*., 1996)	6888 women with breast cancer 9529 population controls (1988–91)	4 US states	Usual occupation from telephone interview; job–exposure matrix	**Potential for exposure** Low Medium High	 577 104 57	 1.0 1.1 1.4	 (0.91–1.2) (0.83–1.4) (0.99–2.1)	Adjusted for risk factors for breast cancer
	1424 women with premenopausal breast cancer 2675 population controls			Low Medium High	91 18 20	0.91 0.82 2.0	(0.69–1.2) (0.45–1.5) (1.0–3.8)	
	5163 women with postmenopausal breast cancer 6421 population controls			Low Medium High	462 78 35	1.0 1.1 1.3	(0.89–1.2) (0.80–1.5) (0.82–2.2)	
USA (Coogan & Aschengrau, 1998)	259 women with breast cancer 738 general population controls (1983–86)	5 Upper Cape Cod towns in MA	Work history from questionnaire; job–exposure matrix	Occupational exposure to medium magnetic fields Occupational exposure to high magnetic fields	16 7	0.9 1.2	(0.5–1.7) (0.4–3.6)	Adjusted for risk factors for breast cancer

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
Sweden (Forssén *et al*., 2000)	1767 women with breast cancer 1766 population controls (1960–65)	Cohort of residents near power lines	Occupation from census; job–exposure matrix	**Occupational exposures** < 0.12 μT 0.12–0.19 μT ≥ 0.20 μT **Occupational and residential exposures** < 0.12 μT = 0.12 μT	 156 178 62 31 8	 1.0 1.0 1.0 1.0 0.9	 (baseline) (0.7–1.4) (0.7–1.6) (baseline) (0.3–2.7)	Matched on age, individual power line and municipality
Men								
USA (Demers *et al*., 1991)	227 men with incident breast cancer 300 population controls (1983–87)	10 US population-based cancer registries	2 occupations of longest duration from questionnaire; occupation	**Any electrical occupation** Ever exposed < 10 years 10–19 years 20–29 years ≥ 30 years	33 10 6 8 9	1.8 1.8 1.8 1.5 2.1	(1.0–3.7) (0.7–4.9) (0.5–6.2) (0.5–4.3) (0.7–6.2)	
USA (Rosenbaum *et al*., 1994)	71 men with incident breast cancer 256 volunteers from cancer screening clinic (1979–88)	Western New York state	Hospital registration cards, city directories; electrical occupations	Electrical occupations	6	0.6	(0.2–1.6)	Adjusted for age, county and heat exposure
Sweden (Stenlund & Floderus, 1997)	63 men with breast cancer 1121 population controls (1985–91)	Cancer registry	Postal questionnaire and spot measurements; job–exposure matrix	**Mean level** ≤ 0.15 μT (Q1) 0.16–0.19 μT (Q2) 0.20–0.28 μT (Q3) ≥ 0.29 μT (Q4) ≥ 0.41 μT	 11 17 17 11 4	 1.0 1.2 1.3 0.7 0.7	 (baseline) (0.6–2.7) (0.6–2.8) (0.3–1.9) (0.2 –2.3)	Adjusted for age, education and exposure to solvents

Table 30 (contd)

Country (reference)	Subjects: cases, controls (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF magnetic fields	No. of cases	Odds ratio (95% CI)		Comments
USA (Cocco *et al*., 1998b)	178 male deaths from breast cancer 1041 male deaths from other causes (controls) (1985–86)	Death certificates	Occupation of longest duration from questionnaire to next-of-kin; job–exposure matrix	**Probability of exposure**				
				Low	30	1.0	(0.6–1.6)	
				Medium	7	1.2	(0.5–3.1)	
				High	19	1.1	(0.6–1.9)	
				Level of exposure				
				Low	31	1.0	(0.6–1.7)	
				Medium	16	1.1	(0.6–2.0)	
				High	9	1.0	(0.5–2.1)	

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ANLL, acute non-lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CNLL, chronic non-lymphocytic leukaemia; MDS, myelodysplastic syndrome; NR, not reported; Q, quartile

[a] This study included five cases of leukaemia not included in the initial analysis by Thériault *et al*. (1994); this explains the different results for Ontario workers reported in the two papers.

[b] Product of potential exposure score and duration in months

Table 31. Case–control studies of occupational groups with assumed or documented exposure to ELF electric fields[a]

Country (reference)	Subjects (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF electric fields	No. of cases	Odds ratio (95% CI)		Comments
Leukaemia								
Canada (Miller *et al*., 1996) [included in Thériault *et al*., 1994][b]	50 men with leukaemia 199 cohort controls (1970–88)	Cohort of electric utility workers at Ontario Hydro	Company personnel records; job–exposure matrix based on magnetic fields and measurements of exposure to electric fields (Positron meter)	Electric fields (V/m–years) 0–171 172–344 ≥ 345	 11 13 26	 1.0 2.1 4.5	 (baseline) (0.59–7.2) (1.0–20)	Adjusted for socioeconomic status and potential occupational confounders
	20 incident cases of ANLL 80 cohort controls			0–171 172–344 ≥ 345	4 6 10	1.0 10 7.9	(baseline) (0.58–172) (0.43–143)	
	19 incident cases of CLL 76 cohort controls			0–171 172–344 ≥ 345	3 6 10	1.0 1.3 7.2	(baseline) (0.07–21) (0.31–169)	
France (Guénel *et al*., 1996) [included in Thériault *et al*., 1994]	72 men with leukaemia 285 cohort controls (1978–89)	Cohort of electric utility workers at Electricité de France	Company personnel records; job–exposure matrix based on measurements of exposure to electric fields (Positron meter)	Electric fields (V/m–years) < 253 253–329 330–401 ≥ 402	 38 20 10 4	 1.0 0.96 0.71 0.37	 (baseline) (0.45–2.0) (0.27–1.9) (0.11–13)	Adjusted for socioeconomic status
	34 men with ANLL 134 cohort controls			percentiles < 50 ≥ 50–< 75 ≥ 75–< 90 ≥ 90	 18 10 4 2	 1.0 0.95 0.71 0.36	 (baseline) (0.45–2.0) (0.26–1.9) (0.10–1.3)	Adjusted for socioeconomic status and exposure to magnetic fields

Table 31 (contd)

Country (reference)	Subjects (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF electric fields	No. of cases	Odds ratio (95% CI)		Comments
USA (Kheifets *et al.*, 1997b) [same study as London *et al.*, 1994]	2355 men with leukaemia 67 212 other cancer cases (1972–90)	Los Angeles county cancer registry	Job at diagnosis from medical record; job–exposure matrix based on measured electric fields in selected occupations	Electric fields (V/m)				
				< 10	2296	1.0	(baseline)	
				10–20	28	1.2	(0.80–1.9)	
				> 20	31	1.2	(0.78–1.7)	
	853 men with ANLL			< 10	831	1.0	(baseline)	
				10–20	11	1.3	(0.68–2.5)	
				> 20	11	1.2	(0.59–2.2)	
	534 men with CLL			< 10	517	1.0	(baseline)	
				10–20	9	1.9	(1.1–3.2)	
				> 20	8	1.3	(0.72–2.2)	
	487 men with CML			< 10	478	1.0	(baseline)	
				10–20	2	0.39	(0.09–1.6)	
				> 20	7	1.3	(0.60–2.8)	
Norway (Tynes *et al.*, 1994b)	52 men with leukaemia 259 cohort controls (1958–90)	Cohort of railway workers	Job history from employment files; job–exposure matrix	Electric fields (kV/m–years)				
				None	19	1.0	(baseline)	
				Low (0.1–5)	9	0.44	(0.18–1.1)	
				High (> 5–30)	24	0.98	(0.48–2.0)	
				Very high (21–30)	3	0.68	(0.18–2.6)	

Table 31 (contd)

Country (reference)	Subjects (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF electric fields	No. of cases	Odds ratio (95% CI)		Comments
Brain tumours								
Norway (Tynes *et al.*, 1994b)	39 men with brain tumours 194 cohort controls (1959–90)	Cohort of railway workers	Job history from employment files; job–exposure matrix	Electric fields (kV/m–years) None Low (0.1–5) High (> 5–30) Very high (21–30)	 11 12 16 4	 1.0 0.69 1.2 1.2	 (baseline) (0.28–1.7) (0.49–2.8) (0.33–4.6)	
Canada (Miller *et al*., 1996) [included in Thériault *et al*., 1994]	24 incident cases of malignant brain tumours 96 cohort controls [exact number not given] (1970–88)	Cohort of electric utility workers at Ontario Hydro	Company personnel records; job–exposure matrix based on electric field exposure measurements (Positron meter)	Electric fields (V/m–years) 0–171 172–344 ≥ 345	 12 4 8	 1.0 0.57 0.99	 (baseline) (0.10–3.2) (0.16–6.2)	Adjusted for socioeconomic status and potential occupational confounders

Table 31 (contd)

Country (reference)	Subjects (recruitment period)	Source of subjects	Source of job information; exposure assessment methods	Estimates of exposure to ELF electric fields	No. of cases	Odds ratio (95% CI)		Comments
France (Guénel *et al*., 1996) [included in Thériault *et al*., 1994]	69 incident cases of brain tumour (ICD-9 191, 225) 271 cohort controls (1978–89)	Cohort of electric utility workers at Electricité de France	Company personnel records; job–exposure matrix based on electric field exposure measurements (Positron meter)	Electric fields (V/m–years) < 238 238–318 319–386 ≥ 387	 29 22 8 10	 1.0 2.5 1.4 3.1	 (baseline) (0.99–6.2) (0.46–4.5) (1.1–8.7)	Adjusted for socioeconomic status
	59 incident cases of malignant brain tumour (ICD-9 191) 231 cohort controls			Percentiles < 50 ≥ 50–< 75 ≥ 75–< 90 ≥ 90		 1.0 2.5 1.6 1.8	 (baseline) (0.93–6.8) (0.46–5.4) (0.54–5.7)	Adjusted for socioeconomic status and exposure to magnetic fields

ANLL, acute non-lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia

[a] Electric field measurements in occupational studies are made using meters that are worn on the body. The results are therefore difficult to interpret because in this situation the field is distorted and the measurement is sensitive to body position.

[b] This study included five cases of leukaemia not included in the initial analysis by Thériault *et al*. (1994); this explains the different results for Ontario workers reported in the two papers.

cancer registry, with four controls per case matched on age and year of registration. For the combined group of selected occupations involving potential exposure to electrical and magnetic fields, a marginally significant excess risk for leukaemia was seen (odds ratio, 1.7; 95% CI, 0.97–3.0) on the basis of 18 observed cases. In an extension of this study to cover the registration period 1980–84, Pearce *et al*. (1989) used 19 904 of 24 762 notified cases of cancer among men ≥ 20 years old for whom information on occupation was available (80% of all relevant registry notifications) to evaluate any link between site-specific cancer and 'electrical work'. For each site of cancer under investigation, other sites formed the control group. 'Electrical work' was associated with an increased risk for leukaemia (odds ratio, 1.6; 95% CI, 1.0–2.5) on the basis of 21 observed cases. The odds ratios were generally greater for chronic leukaemia (odds ratio, 2.1; 95% CI, 1.2–3.8) than for acute leukaemia (odds ratio, 1.3; 95% CI, 0.62–2.5) and the risk was generally greater for subjects aged 65 years or more than for those aged 20–64 years.

In a case–control study based on death certificates recorded in 1985 and 1986 in 16 states in the USA (Loomis & Savitz, 1990), 3400 cases of leukaemia among men ≥ 20 years were compared with approximately 34 000 controls matched on year of death and who had died from causes other than brain cancer or leukaemia. Decedents were allocated to the exposed group if the occupation or industry given on their death certificate indicated that they had held a job included in a predefined list of electrical occupations (Milham, 1982). All other jobs were considered as unexposed. There was no association between electrical occupation and leukaemia (odds ratio, 1.0; 95% CI, 0.8–1.2). A slightly increased risk was observed for acute lymphoblastic leukaemia (odds ratio, 1.5; 95% CI, 0.7–3.4).

Richardson *et al*. (1992) conducted a case–control study of men and women ≥ 30 years old, resident in France. The cases had been diagnosed with acute leukaemia in two hospitals in France between 1984 and 1988; the 561 controls were patients in other departments at the same hospitals, matched to cases for sex, age (± 5 years), ethnic group and place and type of dwelling. Information on past medical history including radiotherapy and chemotherapy, drug use, some sources of environmental exposure and exposure related to leisure activities and a full occupational history described by job titles and industrial activities was obtained by personal interview for 204 cases (72% of those eligible) and 561 controls. Case and control subjects for whom the interviewer had recorded poor cooperation (approximately 5%) and case subjects without controls and vice versa were subsequently excluded, leaving 185 (154 acute myeloid leukaemia and 31 acute lymphoblastic leukaemia) cases (50.2% men) and 513 (48.2% men) controls for analysis. Exposure to ELF electric and magnetic fields, benzene, ionizing radiation, exhaust fumes and pesticides were assessed by an industrial hygienist on the basis of the reported occupational history of each study subject. Whenever possible, the exposure to an agent was coded as either low (< 5% of working time), medium (5–50%) or high (> 50%). There were three electronic engineers among cases and none among controls. After adjusting for prior

chemotherapy or radiotherapy and taking into account the matching variables in an unconditional logistic regression model, any occupational exposure to electric and magnetic fields (all types of exposure) was shown to be associated with an elevated relative risk for acute leukaemia (odds ratio, 1.7; 95% CI, 0.9–3.5; 14 cases), while occupational exposure to ionizing radiation was not (odds ratio, 0.7; 95% CI, 0.2–2.0). Dividing the group of workers exposed to electric and magnetic fields into arc welders and others gave odds ratios of 1.2 (95% CI, 0.5–3.0) for welders and 3.9 (95% CI, 1.2–13) for others, based on eight and seven cases, respectively. [The Working Group noted that the risk estimation made after the separation of sources of exposure to electric and magnetic fields into arc-welding and non-arc-welding should be regarded as a post-hoc analysis. The Working Group also noted that all seven cases of acute leukaemia in workers exposed to electric and magnetic fields from arc-welding were acute myeloid leukaemia and that there was no information on the subtype distribution among the eight cases who were exposed to electric and magnetic fields from sources other than arc-welding.]

A case–control study within a cohort of telephone linemen at the American Telephone and Telegraph company was conducted by Matanoski *et al*. (1993). The cases were deaths from leukaemia, except chronic lymphocytic leukaemia, that occurred from 1975–80 among white men who had worked for the company for at least two years. Deaths were identified from company records for all workers who were still employed by the company when they died and for a subset of retired workers. From 177 eligible cases and their matched controls, a complete job history was obtained in 35 sets, each set was composed of a case plus at least one of its matched controls. The assessment of exposure to magnetic fields was made using the EMDEX-C personal monitor to make measurements on 15–61 individuals in each occupational category (204 measurements at 10-second intervals). No assessment of exposure to other potentially leukaemogenic agents was performed. The odds ratio for exposure above median of the mean values was 2.5 (95% CI, 0.7–8.6) compared with exposure below median of the mean values. There was also an indication of a dose–response relationship when subjects were divided into quartiles of peak exposure. [The Working Group noted that little weight should be given to a study in which only 35 of 177 eligible cases were included. It is not listed in Table 30.]

In a hospital-based case–control study conducted in one hospital in northern Italy, 46 men and 40 women aged between 15 and 74 years who had been newly diagnosed during 1989–90 with myeloid leukaemia (acute and chronic) or myelodysplastic syndrome were identified (Ciccone *et al*., 1993). Two control groups were chosen, one selected from all patients newly diagnosed with other diseases at the same hospital and one selected from the city population in the area of the hospital. Both groups were frequency-matched to the cases on sex, age and area of residence. The response rates were 91% for cases, 99% for the hospital controls and 82% for the population controls, leaving 86 cases (50 patients with acute myeloid leukaemia, 17 with chronic myeloid leukaemia and 19 with myelodysplastic syndrome) and 246 controls for analysis. The

occupational history of the study subjects was used by one industrial hygienist to assess the probability of exposure to ELF electric and magnetic fields and to eight other agents or classes of agent known or suspected to increase the risk for myeloid leukaemia, myelodysplastic syndrome or other haematolymphopoietic malignancies. Using logistic regression analysis, male study subjects possibly or probably exposed to electric and magnetic fields had a non-significantly increased odds ratio of 1.6 (95% CI, 0.6–4.1) for myeloid leukaemia or myelodysplastic syndrome combined, compared with subjects not exposed to electric and magnetic fields or any of the other risk factors under study. The equivalent risk estimate for women was 0.8 (95% CI, 0.2–2.5). The estimates were based on 17 men and four women who had been exposed to electric and magnetic fields.

In a cohort study of cancer mortality in 36 221 electricity utility workers who had been employed at the Southern California Edison Company for at least one year between 1960 and 1988, the main analyses used a nested case–control study design, based on 3125 identified causes of death at the end of the follow-up period in 1988 (Sahl *et al*., 1993). Magnetic fields were measured over 776 person–days in 35 occupational categories using the EMDEX-2 meter. Case–control analyses were presented for 44 cases of leukaemia, but no association with scores for exposure to magnetic fields was observed (mean, median, 99th percentile, fraction above different thresholds). In a re-analysis of these data based on different exposure categories, a modest non-significantly increased risk for leukaemia was apparent (Kheifets *et al*., 1999).

Within a well-defined population of men who, according to the 1980 census, were employed and living in mid-Sweden, Floderus *et al*. (1993) conducted a study of all men aged 20–64 years notified to the Swedish Cancer Registry with a recent diagnosis of leukaemia (n = 426) during 1983–87. For the control group, two subjects per case (n = 1700) were chosen from the source population and matched to the case on age. Only acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia and chronic lymphocytic leukaemia were included. A postal questionnaire was used in which a full employment history was requested, including a description of all major work tasks undertaken by the study subject during the 10-year period before the diagnosis (and the equivalent dates for the controls). The questionnaire was completed by 77% of leukaemia patients or their relatives and 72% of the control subjects who received the questionnaire, so that 250 leukaemia cases and 1121 controls were available for analysis. On the basis of the work task held for the longest time by 1015 cases and control participants, a full-day measurement of exposure to ELF electric and magnetic fields at a frequency of 50 Hz was conducted using EMDEX-100 and EMDEX-C meters. Exposure categories were defined on the basis of the quartiles of exposure levels measured among the control subjects. The evaluation of exposure to potential confounders (benzene, other solvents, ionizing radiation and smoking) was based on self-reported information from study subjects and workplace information. On the basis of the job held for the longest time during the l0-year period before diagnosis, the age-adjusted odds ratios for all types of leukaemia combined were 0.9 (95% CI,

0.6–1.4), 1.2 (95% CI, 0.8–1.9) and 1.6 (95% CI, 1.1–2.4) among study subjects with daily mean level of exposure to magnetic fields in the second (0.16–0.19 μT), third (0.20–0.28 μT) and upper (≥ 0.29 μT) exposure quartiles, respectively, when compared with the risk of subjects with exposure in the lower quartile (≤ 0.15 μT). In an extended analysis on leukaemia subtypes, the excess risk seemed to be due exclusively to an increased risk for chronic lymphocytic leukaemia, with an odds ratio for exposure in the upper quartile of 3.0 (95% CI, 1.6–5.8). With exposure above the 90th percentile (≥ 0.41 μT), the odds ratio for chronic lymphocytic leukaemia was 3.7 (95% CI, 1.8–7.7). The results were not changed when potential confounders were taken into consideration; however, no independent risk estimates were given for these potential confounders. [The Working Group noted that the different proportions of postal questionnaires completed by next-of-kin (cases, 67%; controls, 0%) may have affected the odds ratios.]

London *et al*. (1994) conducted a case–control study based on cancer registry data. The cases were 2355 men aged 20–64 years diagnosed with leukaemia, and reported to the population-based cancer registry for Los Angeles county between 1972 and 1990. The controls were 67 212 men diagnosed with other cancers, excluding malignancies of the central nervous system. Only the occupation recorded in the medical record at the time of diagnosis was available to estimate occupational exposure to electric and magnetic fields. The assessment of exposure was based on measurements of magnetic fields obtained for 278 electrical workers in nine electrical occupations and 105 workers in 18 non-electrical occupations selected at random from the general population. The workers selected from each occupational group wore an EMDEX monitor for one work shift. A task-weighted estimate of exposure to magnetic fields in a given occupation was made. A single exposure index was calculated for all non-electrical occupations for which the mean exposure to magnetic fields was generally lower than that in electrical jobs. Occupational exposure to ionizing radiation, benzene, chlorinated hydrocarbon solvents, other solvents and pesticides was evaluated by an expert panel. Using the magnetic field exposure estimates, the odds ratios were 1.0, 1.2 (95% CI, 1.0–1.6) and 1.4 (95% CI, 1.0–2.0), respectively, for exposure to < 0.17 μT, 0.18–0.80 μT and ≥ 0.81 μT, and the trend was statistically significant. An analysis by leukaemia subtype showed a high odds ratio for chronic myeloid leukaemia (odds ratio, 2.3; 95% CI, 1.4–3.8) for average exposure ≥ 0.81 μT, compared with exposure < 0.17 μT, but there was also some evidence of increased risk for acute non-lymphoblastic leukaemia and chronic lymphocytic leukaemia. According to the authors, these results were not appreciably affected by adjustment for other occupational exposures. Data on electric fields were also collected in this study (Table 31). The measurements of electric fields by occupational group revealed no clear evidence of an association between this exposure and leukaemia, and no exposure–response relationship for any leukaemia subtype was seen (Kheifets *et al*., 1997b). [The Working Group noted that the assessment of occupational exposure was based on a single occupation recorded at the time of cancer diagnosis; only a few non-electrical occupations were measured, but they were used as an exposure proxy for all other non-electrical occupations; controls were other

cancer cases: if workers in electrical occupations have a lower incidence of other cancers than non-electrical workers, the odds ratio for leukaemia could be spuriously elevated relative to non-electrical workers. It was also noted that the cut-points used for the categorization of exposure correspond to the 97% and 99% percentile in the control population. No clear explanation was given for this apparently unusual choice.]

Tynes *et al*. (1994b) conducted a case–control study of leukaemia nested in a cohort of 13 030 male railway line workers, exposed to 16 2/3-Hz electric and magnetic fields, outdoor station workers and railway electricity workers (railway electricity line workers, installation electricians, radio communication workers and railway power substation workers) selected from the records of all employees working on either electric or non-electric railways in Norway in 1957 and from historical and current databases provided by the railway workers' trade union. The case groups comprised all 52 members (one case was excluded because no work history was available) diagnosed according to the files of the national Norwegian Cancer Registry with leukaemia during the follow-up period 1958–90. Each case was matched on year of birth with four or five controls selected from the cohort (a total of 259 controls). Work histories were combined with a job–exposure matrix for ELF-electric and magnetic fields to provide a simple exposure categorization: i.e. ever exposed versus never exposed to electric railway lines, and a more complex one: i.e. cumulative exposure (μT–year) during a person's entire period of employment (up to the date of diagnosis of cancer or a similar date for the matched controls) with the railways in Norway. Limited information on potential confounders such as exposure to creosote, solvents and herbicides was also collected; information on smoking (ever smokers) was obtained by telephone interviews with the subjects or their work colleagues. Ever exposure to magnetic fields from electric railway lines was associated with an odds ratio of 0.72 (95% CI, 0.37–1.4) for all types of leukaemia combined. An analysis of leukaemia subtypes also showed no association. Using study subjects never exposed to magnetic fields from electric railway lines as the exposure reference category, cumulative exposures of 0.1–310 μT–years (low exposure), 311–3600 μT–years (high) and 1900–3600 μT–years (very high) were associated with odds ratios of 1.0 (95% CI, 0.49–2.1), 0.49 (95% CI, 0.22–1.1) and 0.84 (95% CI, 0.25–2.8), respectively, for leukaemia. Adjustment for smoking habits and potential confounders in a multivariate regression analysis for matched pairs did not change the results. Subanalyses with inclusion of lag time intervals (5 and 15 years) and exposure windows (5–25 years and 2–12 years) did not reveal any associations. Analysis for electric fields did not show any association with leukaemia (see Table 31).

A large case–control study of exposure to magnetic fields nested within three cohorts of electric utility workers in Quebec and Ontario, Canada, and in France was conducted by Thériault *et al*. (1994). There were small differences in study design and the results were not consistent across the three utilities; each cohort is therefore described separately.

In Quebec, the cohort included all men with at least one year of employment at Hydro-Québec, between January 1970 and December 1988. The observation period ended either at death or December 31, 1988. The cases were 774 men from the cohort newly diagnosed with cancer during this period (24 leukaemia). The controls were 1223 cohort members matched to the cases by year of birth with a case–control ratio of 1:4 for cancer of the haematopoietic system, brain cancer and skin melanoma, and 1:1 for all other cancer sites. Measurements of magnetic field exposure were made with a personal Positron meter, worn for a full working week by 466 workers at Hydro Québec, who had been selected to achieve a representative sample of all workers in 32 occupational groups. The time-weighted average exposure to magnetic fields was calculated from the measurements to construct a job–exposure matrix. Past exposure to magnetic fields was estimated using adjustment factors based on changes in power systems, work techniques and exposure sources. Exposure to other potential occupational carcinogens was evaluated through expert judgement. The odds ratio for cumulative exposure to magnetic fields above median (3.1 μT–years) was 0.29 (95% CI, 0.04–1.8) for all leukaemia and 0.75 (95% CI, 0.00–>100) for acute non-lymphoblastic leukaemia, based on small numbers. No clear association with other leukaemia types was observed.

In Ontario, the cohort comprised men with one full year of employment at Ontario Hydro between 1973 and 1988, as well as men on the pension roll in 1970–73. The observation period ended at death or December 31, 1988. A total of 1472 incident cancer cases (45 leukaemia) were identified from the Ontario Cancer Registry during the study period. The controls were 2080 men selected in the same way as those from Hydro Québec. Measurements of exposure to magnetic fields were made for 771 workers with 260 job titles. The occupations were then combined in 17 broad categories, based on mean exposure, occupational profiles and consideration of past changes in these factors. These 17 occupational categories were used as the rows of the job–exposure matrix on magnetic fields. Exposure to other occupational agents ((2,4-dichlorophenoxy)acetic acid, (2,4,5-trichlorophenoxy)acetic acid and benzene) was assessed from consultation with experts (Miller *et al.*, 1996). The odds ratio for cumulative exposure to magnetic fields above 3.1 μT–years was 3.1 (95% CI, 1.1–9.7) for all leukaemia and 6.2 (95% CI, 0.95–78) for acute non-lymphoblastic leukaemia. Non-significant increases in odds ratios were also observed for chronic lymphocytic leukaemia.

In France, the cohort included men with at least one year of employment at Électricité de France–Gaz de France during 1978–89. The cases were 1905 men identified from company medical records who were newly diagnosed with cancer (71 leukaemia) during the same period. This group of cases included all workers diagnosed with cancer while they were active in the company. Since the identification of cases was not possible for cancer diagnosed after retirement, the observation period ended at termination of employment or December 1989. The controls were 2803 subjects matched to the cancer cases by year of birth in the same way as in the cohort of Hydro Québec workers. The method of assessment of exposure to magnetic fields was similar to that used in Quebec.

Measurements were made using a Positron meter worn by 829 workers for a full working week, selected from 37 occupational groups defined *a priori*. Past exposure to magnetic fields was assessed using adjustment factors. Estimates of exposure to other potential occupational carcinogens were also evaluated using expert judgement in a separate job–exposure matrix. The odds ratios for cumulative exposure to magnetic fields above 3.1 μT–years were 1.4 (95% CI, 0.61–3.1) for all leukaemia and 1.8 (95% CI, 0.57–5.4) for acute non-lymphoblastic leukaemia.

For the three cohorts combined, the odds ratios for all leukaemia were 1.5 (95% CI, 0.90–2.6) for cumulative exposure to magnetic fields above median (3.1 μT–years) and 1.8 (95% CI, 0.77–4.0) for exposure above the 90th percentile (15.7 μT–years). The odds ratios for acute non-lymphoblastic leukaemia were 2.4 (95% CI, 1.1–5.4) and 2.5 (95% CI, 0.70–9.1), respectively. However, there was no clear trend of increased risk with increasing exposure. Elevated odds ratios were also observed for chronic lymphocytic leukaemia for cumulative exposure during the 20 years prior to diagnosis (Thériault *et al.*, 1994).

Data from the Ontario Hydro cohort were re-analysed (Miller *et al*., 1996). This re-analysis included five additional cases of leukaemia not considered in the initial analysis by Thériault *et al*. (1994) (a total of 50 cases). A refined assessment of exposure to potential occupational confounders was also used. The odds ratio for all leukaemia decreased from 2.0 to 1.7 (95% CI, 0.58–4.8) for cumulative exposure between 3.2 and 7 μT–years and from 2.8 to 1.6 (95% CI, 0.47–5.1) for cumulative exposure ≥ 7.1 μT–years, after adjustment for potential occupational confounders. For acute non-lymphoblastic leukaemia, the corresponding odds ratios were reduced from 3.0 to 1.9 (95% CI, 0.27–14) and from 5.0 to 2.9 (95% CI, 0.42–20), respectively. This report also described the risk for leukaemia in relation to exposure to electric fields which were also measured by the Positron meter (Table 31). For leukaemia, the odds ratios for cumulative exposure to electric fields between 172 and 344 V/m–years and for exposure ≥ 345 V/m–years, as compared with exposure below 172 V/m–years (median), were 2.1 (95% CI, 0.59–7.2) and 4.5 (95% CI, 1.0–20), respectively, after adjustment for potential occupational confounders. For acute non-lymphoblastic leukaemia, and the main component, acute myeloid leukaemia, the odds ratios associated with electric fields were elevated but did not reach statistical significance. Analysis of the combined effects of electric and magnetic fields showed that exposure to electric fields carried a greater risk for leukaemia than exposure to magnetic fields. It was shown that risk for leukaemia was more particularly associated with duration of exposure above the exposure threshold (Villeneuve *et al*., 2000).

The effects of electric fields were also investigated among electric utility workers from France. These workers were part of the Canada–France study (Thériault *et al*., 1994). Electric fields were recorded by a Positron meter at the same time as magnetic fields and were used to assess the exposure to electric fields by occupation in a job–exposure matrix (Guénel *et al*., 1996). No association between cumulative exposure to electric fields and leukaemia was observed in this study (Table 31).

Feychting *et al.* (1997) looked at combined residential and occupational exposure (see section 2.3.1).

In an Italian study, Pulsoni *et al*. (1998) compared selected characteristics of 335 patients with acute promyelocytic leukaemia aged > 15 years with those of 2894 patients aged > 15 years diagnosed with other acute myeloid leukaemia. Patients were identified from the files of a clinical database, initiated in 1992, until 1997. A significant association was found between working as an electrician and development of acute promyelocytic leukaemia with an age-adjusted odds ratio of 4.4 (95% CI, 2.0–9.7). [The Working Group noted that the occupational group considered (i.e. electricians) comprised less than 1% of the comparison group of other acute myeloid leukaemia patients making interpretation difficult.]

(ii) *Brain tumours* (see Table 30)

Brain tumours without further histological classification represent a heterogeneous group of lesions. Studies based on death certificates only may include deaths from secondary tumours that have metastasized from an unknown primary cancer, or tumours that are histologically benign (Percy *et al.*, 1981). Where possible the results reported here are specifically for malignant tumours or for known histological types.

Death certificates for white men in Maryland who died between 1969 and 1982 were used to conduct a case–control study on brain tumours (Lin *et al*., 1985). A total of 951 men aged ≥ 20 years who had died from a tumour of the brain (519 gliomas, glioblastoma multiforme, or astrocytomas) were matched by age and date of death with controls who had died from non-malignant diseases. The occupation recorded on the death certificate was used to classify the subjects according to a predefined category of exposure to electric and magnetic fields (definite, probable, possible or no exposure). Jobs were classified according to a list of ‘electrical occupations’ revised from that of Milham (1982). Using the no-exposure group as referent, the odds ratios for primary brain tumours increased with increasing probability of exposure to electric and magnetic fields.

Speers *et al*. (1988) conducted a study based on mortality data in East Texas, USA during the period 1969–78. The cases were 202 white male decedents between 35 and 79 years of age who had been diagnosed with glioma. The controls were 238 men selected from among white residents of the East Texas study area who had died from a cause other than brain tumour. Information abstracted from the death certificate included the usual occupation for which exposure to electric and magnetic fields was classified using the system proposed by Lin *et al*. (1985). The analysis by level of exposure to electric and magnetic fields yielded an increase in risk with increasing probability of exposure with a significant linear trend.

In a cancer registry-based study in New Zealand, Pearce *et al*. (1989) used 19 904 cases of cancer notified from 1980–84 among men ≥ 20 years old, for whom information on occupation was available (80% of all relevant registry notifications) to evaluate any link between site-specific cancer and ‘electrical work’. For each site of

cancer studied, patients with cancer at other sites formed the control group. Among 481 patients with brain cancer (ICD-9 191), 12 had been employed in electrical work, giving an odds ratio for brain tumours of 1.0 (95% CI, 0.56–1.8) on the basis of the 12 observed cases.

Preston-Martin *et al*. (1989) conducted a case-control study on brain tumours in Los Angeles county, USA. The cases were men 25–69 years of age for whom a first diagnosis of glioma or meningioma had been made during 1980–84. Two hundred and seventy-two of 478 eligible cases (202 gliomas and 70 meningiomas) and 272 controls were available for analysis. A complete work history was obtained for each subject, together with information on previous brain diseases, head traumas, alcohol and tobacco habits and diet. Work in an occupation with suspected exposure to electric and magnetic fields, according to Milham's definition (Milham, 1982), was associated with an increased odds ratio for glioma (1.8; 95% CI, 0.7–4.8), and the risk increased with increase in the number of years spent working in these occupations. The association was strongest for astrocytoma (odds ratio, 4.3; 95% CI, 1.2–16) for > 5 years). The authors noted that confounding from occupational exposure to other harmful agents (e.g. solvents) may be an alternative explanation for this finding. [The Working Group noted that selection bias may have occurred because only living patients could be interviewed.]

The study by Loomis and Savitz (1990) based on death certificates in 16 states in the USA, described in the section on leukaemia, also presented results for brain cancer. The cases were 2173 deaths in men from brain cancer (ICD-9 191). The controls were selected from among men who had died from other causes with a 10:1 ratio. Men who were reported to have been electrical workers on their death certificates had an odds ratio of 1.4 (95% CI, 1.1–1.7) when compared with non-electrical occupations.

Ryan *et al.* (1992) also looked at exposure to ELF electric and magnetic fields in the electrical and electronics industries and found no increase in glioma and meningioma.

Floderus *et al*. (1993) (described in the section on leukaemia) conducted a case–control study of all individuals with a recent diagnosis of brain tumour (n = 424) during 1983–87. Only patients with histologically confirmed astrocytoma (type I-IV) or oligodendroglioma were included. A questionnaire was completed by 76% of patients or their relatives and 72% of control subjects, leaving 261 cases of brain tumour and 1121 controls for analysis. Exposure was defined as in the section on leukaemia (p. 215). On the basis of the 10-year period before diagnosis, the age-adjusted odds ratios for all types of brain tumour combined were 1.0 (95% CI, 0.7–1.6), 1.5 (95% CI, 1.0–2.2) and 1.4 (95% CI, 0.9–2.1) among study subjects with a daily mean exposure to electric and magnetic fields in the second (0.16–0.19 μT), third (0.20–0.28 μT) and upper (≥ 0.29 μT) exposure quartiles, respectively, when compared with the lower quartile (≤ 0.15 μT). When exposure was above the 90th percentile (≥ 0.41 μT), the odds ratio was 1.2 (95% CI, 0.7–2.1). The results were unchanged when the potential confounders were taken into consideration. [The Working Group

noted that the different proportions of postal questionnaires completed by next-of-kin; for cases (85%) and for controls (0%) may have affected the odds ratios.]

In a study on cancer mortality among employees at the Southern California Edison Company described in the section on leukaemia (Sahl *et al*., 1993), brain cancer (ICD-9 191) (31 cases) was also investigated and the results are summarized in Table 30. No association between brain cancer mortality and scores of exposure to magnetic fields was apparent.

The Canada–France study on electric utility workers, described in the section on leukaemia (Thériault *et al*., 1994), also presented results for brain cancer (ICD-9 191); they are shown in Table 30. For the three cohorts combined, the odds ratios for all brain cancers were 1.5 (95% CI, 0.85–2.8) for cumulative exposure to magnetic fields above median (3.1 μT–years) and 2.0 (95% CI, 0.76–5.0) for exposure above the 90th percentile (15.7 μT–years). In the analysis by histological subtype, the risk for astrocytoma was particularly elevated in the highest exposure category (odds ratio, 12; 95% CI, 1.1–144), but this result was based on only five exposed cases, and according to the authors was dependent on the statistical method used.

The association between malignant brain cancer and electric fields among workers at Ontario Hydro was investigated by Miller *et al*. (1996) (Table 31). No association between exposure to electric fields and brain cancer was apparent.

The relationship between exposure to electric fields and risk of brain tumour (ICD-9 191, 225) (59 malignant and 10 benign cancers) was also investigated in workers at Électricité de France (Table 31) (Guénel *et al*., 1996), who were part of the Canada–France study described above. Using the arithmetic mean of electric field measurements obtained with the Positron meter, the odds ratio in the highest exposure category was 3.1 (95% CI, 1.1–8.7), but the risk did not increase monotonically with exposure. There was no clear indication of an increased risk when exposure was assessed using the geometric mean of electric fields.

In parallel to the leukaemia study described above, Tynes *et al*. (1994b) conducted a case–control study of brain tumours (unspecified) nested in a cohort of 13 030 male railway workers. The case group comprised all 39 cohort members diagnosed according to the files of the national Norwegian Cancer Registry with brain tumour, during the follow-up period 1958–90. Each case was matched on year of birth with four or five controls selected from the cohort (a total of 194). Ever exposure to electric railway lines was associated with an odds ratio of 0.82 (95% CI, 0.38–1.8) for brain tumours. Using study subjects who had never been exposed to electric railway lines as the exposure reference category, cumulative exposure to magnetic fields of 0.1–310 μT–years (low exposure), 311–3600 μT–years (high) and 1900–3600 μT–years (very high) were associated with odds ratios for brain tumours of 0.81 (95% CI, 0.33–2.0), 0.94 (95% CI, 0.39–2.3) and 0.97 (95% CI, 0.24–4.0), respectively. Subanalyses with inclusion of lag time intervals (5 and 15 years) and exposure windows (5–25 years and 2–12 years) did not reveal any associations. No association between brain tumours and exposure to electric fields was apparent (see Table 31).

In a case–control study nested within a cohort of male members of the US Air Force with at least one year of service in the period 1970–89, 230 cases of brain tumour (ICD-9 191) were matched on year of birth and race with 920 controls (Grayson, 1996). Complete job histories were linked to a job–exposure matrix that assessed the probability of exposure to ELF electric and magnetic fields (definite, probable, possible or no exposure) by job title and time of employment. The odds ratio for workers ever exposed to ELF electric and magnetic fields was 1.3 (95% CI, 0.95–1.7). However, no clear trend relating risk for brain tumour to cumulative exposure was apparent.

In a substudy from Sweden, Feychting *et al.* (1997) estimated the separate and combined effects of occupational and residential exposure to ELF magnetic fields on the risk for tumours of the central nervous system (see section 2.3.1 on residential exposure).

Mortality from brain cancer was investigated by Harrington *et al.* (1997) in a case–control study nested in a cohort of 84 018 men and women employed for at least six months between 1972 and 1984 as electricity generation and transmission workers at the Central Electricity Generating Board of England and Wales. Computerized work histories were available for a part of the cohort from 1972 and for all cohort members from 1979. Follow-up of cohort members until the end of 1991 in the national mortality files revealed a total of 176 deaths from brain cancer of which 112 were confirmed through the national cancer registry as primary brain cancers (case group). Approximately six controls per case were chosen from the cohort and matched to the corresponding case on sex and date of birth, giving a total of 654 controls who were all alive at the date of diagnosis of the corresponding case. Exposure assessment was based on an earlier set of measurements of exposure to ELF electric and magnetic fields (50 Hz) in the electricity supply industry made for 675 person–work shifts (Merchant *et al.*, 1994); the cumulative exposure was categorized into tertiles on the basis of the distribution among all study subjects. Using the study subjects in the lower tertile of cumulative exposure to electric and magnetic fields as the exposure reference category (≤ 3.0 μT–years), study subjects in the middle and upper tertiles had odds ratios for primary brain cancer of 1.3 (95% CI, 0.75–2.2) and 0.91 (95% CI, 0.51–1.6), respectively. Subjects who could not be classified according to their cumulative exposure had an odds ratio of 1.8 (95% CI, 0.93–3.6). There was no significant association between the risk for brain cancer and any of the potential confounders included in the study.

In an update of this cohort study, Sorahan *et al.* (2001) analysed brain tumour mortality until 1997 for the subset of 79 972 study subjects for whom computerized work histories were available for the period 1971–93. A Poisson regression analysis showed age- and sex-adjusted relative risks for death from brain tumour of 0.88 (95% CI, 0.53–1.5), 0.65 (95% CI, 0.41–1.0), 0.68 (95% CI, 0.42–1.1) and 0.68 (95% CI, 0.33–1.4) among cohort members with a lifetime exposure to magnetic fields of 2.5–4.9, 5.0–9.9, 10.0–19.9 and ≥ 20.00 μT–years, respectively, compared with the risk for death from brain tumour among workers with cumulative exposure ≤ 2.4 μT–years.

A re-analysis using the most recent five years of exposure to ELF magnetic fields did not change the results substantially.

In a small study from Sweden, Rodvall *et al*. (1998) identified 105 histologically confirmed cases of intracranial glioma (ICD-9 191) and 26 of meningioma (ICD-9 192.1), newly diagnosed in men aged 25–74 years during 1987–90. The cases were identified from the files of a large university hospital and the regional cancer registry. A total of 155 controls was selected from population listings and matched to the cases on date of birth and parish. Only controls who were alive at the time of diagnosis of the corresponding case were included. A postal questionnaire requesting data on the occupational history of the study subjects was completed for 84 (80%) of the glioma cases (71 by the patient and 13 by a close relative), 20 (77%) of the meningioma cases (19 by the patient and one by a close relative) and, after the inclusion of a number of replacement controls, by 155 [response rate unknown] of the control subjects themselves. The analyses used multiple logistic regression models with adjustment for socioeconomic status and self-reported occupational exposure to solvents and plastic materials. Ever having worked in an electrical occupation was associated with odds ratios of 1.0 (95% CI, 0.4–2.4) for glioma and 1.8 (95% CI, 0.3–3.6) for meningioma. Employment in a job classified by an electrical engineer as probably highly exposed to magnetic fields showed odds ratios of 1.6 (95% CI, 0.6–4.0) for glioma and 2.1 (95% CI, 0.4–10) for meningioma. Risks were also analysed according to the exposure to electric and magnetic fields classified using a previously constructed job–exposure matrix for ELF electric and magnetic fields (Floderus *et al*., 1993, 1996), applied to the job history of the study subjects. Ever having been in an occupation with exposure to magnetic fields > 0.4 μT was associated with odds ratios of 1.9 (95% CI, 0.8–5.0) and 1.6 (95% CI, 0.3–10) for glioma and meningioma, respectively.

Mortality data including all death certificates from 24 US states for the period 1984–92 were used to explore the association of industry and occupation with risk for brain cancer (Cocco *et al*., 1998a). The cases were 28 416 subjects ≥ 25 years old who had died from cancer of the brain (ICD-9 191) and other parts of the central nervous system (ICD-9 192), and the controls were 113 664 subjects who had died from non-malignant diseases other than those affecting the central nervous system, frequency-matched to cases by state, race, sex and age. The subjects were classified as having been exposed or unexposed to electric and magnetic fields and other potential risk factors for brain cancer (herbicides, other pesticides, solvents, lead, contact with animals, contact with the public) using an a-priori job–exposure matrix. Brain cancer showed a consistent association with high socioeconomic status. Exposure to electric and magnetic fields was not associated with risk in any sex–race strata, although an odds ratio of 1.2 (95% CI, 0.9–1.6) was observed among African-American women.

In a re-analysis of 12 980 women based on death certificates, and a refined job–exposure matrix using exposure scores for probability and intensity of exposure, the odds ratio for tumours of the central nervous system was 1.2 (95% CI, 1.1–1.2) for women with any exposure to electric and magnetic fields. Slightly increased odds ratios

of 1.2–1.3 were observed for high exposure probability or high exposure intensity (Cocco *et al.*, 1999).

(iii) *Pooled analysis* (leukaemia and brain tumours)

A pooled analysis of the data from three studies of electric utility workers (Sahl *et al.*, 1993, California, USA; Thériault *et al.*, 1994, France, Ontario, Quebec; Savitz & Loomis, 1995, USA) including four companies and five utilities where quantitative measurements of magnetic fields had been carried out, was conducted to examine the relation between cumulative exposure to magnetic fields and risk of leukaemia and brain tumours (Kheifets *et al.*, 1999). Overall, excluding the data for Ontario, the results indicated a small increase in risk for both brain cancer (relative risk, 1.8; 95% CI, 1.1–2.9) and leukaemia (relative risk, 1.4; 95% CI, 0.85–2.1) for exposure > 16 μT–years as compared to exposure < 4 μT–years. For a 10 μT–year increase in exposure, the relative risks were 1.12 (95% CI, 0.98–1.3) and 1.09 (95% CI, 0.98–1.2) for brain cancer and leukaemia, respectively. There was some consistency of the results across the utility companies.

(iv) *Female breast cancer*

Breast cancer was analysed using the mortality database of 24 US states for the period 1985–89 in a case–control study (Loomis *et al.*, 1994b). After exclusion of 'homemakers', the cases were 28 434 women > 19 years old whose underlying cause of death had been breast cancer and the controls were 113 011 women who had died from other causes, excluding brain cancer and leukaemia. The usual occupation as recorded on their death certificates was used to classify women according to the likelihood of having been exposed to electric and magnetic fields, using an extended list of 'electrical occupations'. The odds ratio for the association between electrical occupation and cancer, adjusted on race and social class, was 1.4 (95% CI, 1.0–1.8).

The same US mortality database was analysed by Cantor *et al*. (1995) using an alternative method for exposure assessment. The study included 33 509 women who had died from breast cancer and 117 794 controls selected from women who had died from causes other than cancer. Exposure scores were determined for each occupation using different indices for levels of exposure to ELF electric and magnetic fields and exposure probability. The results were presented separately for black and white women. There was no consistent excess risk with increasing level or probability of exposure to ELF electric and magnetic fields.

Coogan *et al*. (1996) conducted a case–control study of 6888 (81%) respondent cases out of 8532 eligible women ≤ 74 years of age with breast cancer diagnosed between April 1988 and December 1991 in Maine, Massachusetts, New Hampshire and Wisconsin. The controls were 9529 (84%) respondents out of 11 329 eligible women, frequency-matched on age and state of residence, and identified from driver's license and the lists of the Health Care Financing Administration. Because all subjects were interviewed by telephone, a listed telephone number was required for eligibility by both

cases and controls. The women were asked about their usual occupation, which was classified into one of four categories of potential exposure to 60-Hz magnetic fields (high, medium, low and background exposure), as defined by an industrial hygienist. Compared to women with background exposure, an odds ratio of 1.4 (95% CI, 1.0–2.1) was found for women whose usual occupation was in the high exposure category. The odds ratios for the medium and low exposure categories did not differ appreciably from unity. No significant difference was seen between pre- and post-menopausal women (odds ratio, 2.0 (95% CI, 1.0–3.8) and odds ratio, 1.3 (95% CI, 0.82–2.2), respectively) in the highest exposure groups.

Coogan and Aschengrau (1998) carried out a case–control study on 259 of the 334 women residing in the Upper Cape Cod area who were diagnosed with breast cancer in 1983–86. They selected 738 controls by random-digit dialling, from lists of Medicare beneficiaries or from the death certificates of women who had lived in the same area. Complete work histories were obtained for each subject, and jobs were classified according to their potential for higher than background exposure to magnetic fields (high, medium or no exposure). Residential exposure to magnetic fields from power lines and substations was also considered, as well as exposure to magnetic fields from electrical appliances in the home. Suspected or established risk factors for breast cancer were included in the analyses as potential confounders. There was no association between breast cancer risk and occupational exposure to magnetic fields, nor with any other source of magnetic fields. The adjusted odds ratios for jobs with potential exposure to high electric and magnetic fields and jobs with potential exposure to medium electric and magnetic fields were 1.2 (95% CI, 0.4–3.6) and 0.9 (95% CI, 0.5–1.7), respectively. No association was observed with duration of employment in these occupational groups.

In a study from Sweden, Forssén *et al*. (2000) estimated the separate and combined effects of occupational and residential exposure to ELF magnetic fields on the risk for female breast cancer (see section 2.3.1). Occupational exposure data were available for 744 cases and 764 controls and both contemporary residential and occupational exposure data were available for 197 cases and 200 controls. No increased risk in breast cancer was associated with occupational exposure to ELF magnetic fields.

(v) *Male breast cancer*

Demers *et al*. (1991) investigated occupational exposure to ELF electric and magnetic fields in 227 incident cases of breast cancer in males, 22–90 years old, identified in 1983–87 in 10 population-based cancer registries in the USA (320 cases were eligible). Three hundred controls matched on age and study area (out of 499 eligible controls) were selected by random-digit dialling for controls aged under 65 years and from Medicare lists for older controls. Personal interviews using a standardized questionnaire were used to obtain a partial work history (information on the two longest-held occupations). The estimates of exposure to electric and magnetic fields were based on job titles. Data on several suspected risk factors for male breast

cancer were also collected. The odds ratio associated with jobs entailing exposure to electric and magnetic fields was 1.8 (95% CI, 1.0–3.7). No significant trend with increasing duration of employment in an exposed occupation was observed. No confounding by the non-occupational risk factors investigated in the study was observed. [The Working Group noted that the participation rate was low, especially among controls.]

In a case–control study based on mortality data from 24 states in the USA in the period 1985–88, Loomis (1992) analysed 250 males aged < 19 years who had died from breast cancer and approximately 2500 controls, selected from men who had died from other causes and matched by year of death. Four of the cases had an electrical occupation listed on their death certificate (odds ratio, 0.9). [The Working Group noted the limited number of exposed cases.]

Rosenbaum *et al*. (1994) studied 71 incident cases of male breast cancer diagnosed in western New York between 1979 and 1988, and 256 controls selected from men who had been screened for cancer in the Prevention–Detection Clinic (voluntary cancer screening). The cases and controls were resident in the same areas and were matched by race, year of diagnosis or screening and age. Occupational exposure to electric and magnetic fields was evaluated using a job–exposure matrix, based on the assumption that workers in 'electrical occupations' were exposed to higher than background electric and magnetic fields. Exposure to electric and magnetic fields was associated with an odds ratio of 0.6 (95% CI, 0.2–1.6). [The Working Group noted that selection bias may have occurred for controls and information bias for occupation.]

To study the relationship between exposure to ELF magnetic fields and male breast cancer, Stenlund and Floderus (1997) re-used the study design and the control group established five years earlier by Floderus *et al*. (1993) in the previously described study from mid-Sweden of leukaemias and brain tumours. The new study included 92 men who had been diagnosed with breast cancer during 1985–91 in any part of Sweden. Fifteen patients with cancer of the breast were ineligible for study because permission to contact the patient or a relative was not obtained, or because no relatives were identified. The postal questionnaire was completed by the patient or a close relative for 63 of the cases (69%). The response rate for the controls was 72% giving 1121 controls for analysis. Using the same job–exposure matrix as in the original study and following the same strategy of analysis, the authors found odds ratios for breast cancer of 1.2 (95% CI, 0.6–2.7), 1.3 (95% CI, 0.6–2.8) and 0.7 (95% CI, 0.3–1.9) associated with exposure levels to electric and magnetic fields in the second, third and upper quartile, respectively. [The Working Group noted, as did the authors, that the breast cancer cases were not selected from the same study base as that defined for control subjects, implying a possibility for bias in the selection of study subjects.]

In a case–control mortality-based study on male breast cancer, Cocco *et al*. (1998b) used the data of the US national mortality follow-back survey. The cases were 178 men who had died from breast cancer in a sample of 1% of all adult deaths that occurred in the USA in 1986 (excluding Oregon) and all men who had died from breast cancer in

1985 among black and white adults 25–74 years old. The controls were 1041 male decedents selected from men who had died from all other causes of death, after the exclusion of smoking- and alcohol-related causes, and matched on race, age and region of death. Questionnaires were sent to the next-of-kin of the decedents to obtain information on sociodemographic variables; the longest-held occupation and industry, and non-occupational data on consumption of selected dietary items; alcohol consumption, tobacco smoking, and medical history. Occupational exposure to electric and magnetic fields, solvents, herbicides, other pesticides, high temperatures and polycyclic aromatic hydrocarbons was estimated from a job–exposure matrix that included scores for exposure intensity and probability of exposure. Although an increased odds ratio was observed in men with high socioeconomic status, and in certain occupations or industries not classified as having high exposure to electric and magnetic fields, no association was observed with the probability or the intensity of exposure to electric and magnetic fields, organic solvents, polycyclic aromatic hydrocarbons, herbicides and other pesticides.

(vi) *Other cancer sites*

Several other sites of cancer have been investigated in relation to ELF electric and magnetic fields, particularly in case–control studies nested within occupational cohorts of electric utility workers, since data on all sites of cancer were collected in these studies. However, there was generally no indication of an increased risk for any site of cancer other than those already described for leukaemia and brain tumours. The results obtained for the sites of cancer that were considered of interest *a priori* in studies of electric utility workers, namely lymphomas (Sahl *et al*., 1993; Thériault *et al*., 1994) and malignant melanoma (Thériault *et al*., 1994) showed no association with exposure to magnetic fields.

In a population-based case–control study in the four northern counties of Sweden, Hallquist *et al*. (1993) identified a total of 188 surviving patients with thyroid cancer who were aged 20–70 years at the time of diagnosis during 1980–89. The cases were drawn from the national Swedish Cancer Registry and represented 81% of all cases of thyroid cancer notified in persons of the same age group during the period of interest in the four counties (44 patients had other diseases and were excluded). The original histopathological diagnoses were re-evaluated by a pathologist, resulting in the exclusion of seven patients who were reclassified as having diseases other than thyroid cancer. One subject died shortly before the interview, leaving 180 histologically verified cases for study. For each case, two living controls close in age and of the same sex, and resident in one of the four northern counties, were drawn from the national population registry. Information on the occupational history of the study subjects and on known and suspected risk factors for thyroid cancer was obtained through a postal questionnaire that was completed by 171 case subjects (response rate, 95%) (123 women and 48 men), and 325 control subjects (240 women and 85 men) (response rate, 90%). Five male cases had worked as linemen while no controls had reported that occupation. The authors stated that this occupation might entail exposure to ELF

electric and magnetic fields; however, no exposure estimates were given. Three of these linemen were exposed to impregnating agents, i.e. chlorophenols and creosote, which were found in the analysis to be significantly associated with thyroid cancer (odds ratio, 2.8; 95% CI, 1.0–8.6). Employment as an electrical worker was associated with an odds ratio of 1.9 (95% CI, 0.6–6.1) on the basis of eight exposed cases.

In order to study the relationship between exposure to ELF magnetic fields and testicular cancer, Stenlund and Floderus (1997) re-used the study design and the control group established five years earlier by Floderus *et al*. (1993) in the previously described study from mid-Sweden of leukaemias and brain tumours. The extended study included 214 men diagnosed with testicular cancer during 1983–87 and living in the original catchment area. The postal questionnaire was completed by the patient [proportion not given] or a relative [proportion not given] for 144 of the 185 eligible subjects with testicular cancer (78%). The response rate among the controls was 72% leaving 1121 controls. Using the same job–exposure matrix as in the original study and following the same strategy of analysis, the authors found odds ratios for testicular cancer of 1.3 (95% CI, 0.7–2.4), 1.4 (95% CI, 0.8–2.7) and 1.3 (95% CI, 0.7–2.5) associated with exposure to magnetic fields in the second, third and upper quartile (0.16–0.19 μT, 0.20–0.28 μT and ≥ 0.29 μT), respectively. Among the 13% of study subjects who were exposed to the highest estimated levels (≥ 0.41 μT), the odds ratio for testicular cancer was 2.1 (95% CI, 1.0–4.3). In a subsequent analysis on subtypes of testicular cancer, the authors observed an increased risk for non-seminomas particularly in subjects less than 40 years of age (odds ratio, 7.1 (95% CI, 1.4–36), odds ratio, 7.1 (95% CI, 1.3–38), odds ratio, 8.1 (95% CI, 1.7–39) and odds ratio, 16 (95% CI, 2.7–95) in the four exposure quartiles, respectively).

3. Studies of Carcinogenicity in Experimental Animals

3.1 Chronic exposure studies

The results of one- and two-year rodent bioassays are summarized in Table 32.

3.1.1 *Mouse*

Groups of 100 male and 100 female B6C3F_1 mice, six to seven weeks of age, were exposed for 18.5 h per day for two years to linearly polarized 60-Hz magnetic fields that were nearly pure, transient-free and had less than 3% total harmonic distortion. [The group-size used in this study was twice that commonly used in chronic rodent bioassays; this enlargement was purposely chosen to increase the statistical power of the experimental design, and thereby increase its ability to identify potentially weak carcinogenic effects (Portier, 1986).] Groups of animals were continuously exposed to field strengths of 2 μT, 200 μT or 1000 μT, or were intermittently exposed (1 h on/1 h off for 18.5 h per day) to a field strength of 1000 μT. Parallel sham control groups were housed within an identical exposure apparatus, but were exposed only to ambient magnetic fields. The exposure system has been described by Gauger *et al.* (1999). The design of these studies allowed for continuous monitoring of magnetic field strength and waveform throughout the two-year exposure period. At termination, all animals received a full necropsy and complete histopathological evaluations were performed on all gross lesions collected from all study animals, in addition to examinations of 43 tissues per animal in all study groups. Body weights were comparable in all groups, but a statistically significant reduction in survival time was observed in male mice subjected to continuous exposure to field strengths of 1000 μT. (This effect was not seen in female mice.) When compared to controls, no increases in the incidence of neoplasms at any site were observed in males or females from any treated group. In fact, a statistically significant reduction in the incidence of malignant lymphoma was observed in female mice exposed intermittently to 1000 μT (32/100 in controls versus 20/100; $p = 0.035$) and significant decreases in the combined incidence of lung tumours were observed in both male (30/100 in controls versus 19/100; $p = 0.04$) and female mice (11/95 in controls versus 2/99; $p = 0.008$) exposed to field strengths of 200 μT. In addition, statistically significant reductions in the total incidence of malignant neoplasms (all sites) were seen in female mice continuously exposed to field strengths of 200 μT (55/100 in controls versus 39/100;

Table 32. Summary of statistically significant findings ($p < 0.05$) from one- and two-year rodent bioassays on carcinogenicity of magnetic fields

Reference	Animal model (species/strain/sex)	Exposure (frequency: field strength)	Statistically significant differences from sham controls (tumour type, trend, field strength)	Comment
McCormick *et al.* (1999); National Toxicology Program (1999a)	Mouse/B6C3F$_1$/ male	60 Hz: 2 μT, 200 μT, 1000 μT or 1000 μT-intermittent	Lung tumours, ↓, 200 μT	
	Mouse/B6C3F$_1$/ female		Malignant lymphoma, ↓, 1000 μT-intermittent Lung tumours, ↓, 200 μT Malignant neoplasms, all sites, ↓, 200 μT Malignant neoplasms, all sites, ↓, 1000 μT	
Mandeville *et al.* (1997)	Rat/Fischer 344/ female (F_0, F_1)	60 Hz: 2 μT, 20 μT, 200 μT, 2000 μT	None	
Yasui *et al.* (1997)	Rat/Fischer 344/ male	50 Hz: 500 μT, 5000 μT	Fibroma of subcutis, ↑, 5000 μT Invasive neoplasms (all), ↓, 500 μT	Histopathology limited to gross lesions identified at necropsy
	Rat/Fischer 344/ female		None	Histopathology limited to gross lesions identified at necropsy
Boorman *et al.* (1999a); National Toxicology Program (1999a)	Rat/Fischer 344/ male	60 Hz: 2 μT, 200 μT, 1000 μT or 1000 μT-intermittent	Leukaemia, ↓, 1000 μT-intermittent Preputial gland carcinoma, ↑, 200 μT Skin trichoepithelioma, ↑, 1000 μT Thyroid C-cell tumours, ↑, 2 μT Thyroid C-cell tumours, ↑, 200 μT Thyroid C-cell carcinoma, ↑, 2 μT	
	Rat/Fischer 344/ female		Adrenal cortex-adenoma, ↓, 1000 μT-intermittent	

↑, increase; ↓, decrease

$p = 0.015$) and 1000 μT (55/100 in controls versus 40/100; $p = 0.024$) (McCormick *et al*., 1999; National Toxicology Program, 1999a).

In a site-specific chronic bioassay, a group of 380 female C57BL/6 mice was exposed to a circularly polarized 60-Hz magnetic field at a field strength of 1420 μT for up to 852 days. The incidence of haematopoietic neoplasms in these mice was compared with that observed in a negative (untreated) control group of 380 female C57BL/6 mice and in a sham-treated control group of 190 female C57BL/6 mice. Chronic exposure to magnetic fields had no statistically significant effects on animal survival or on the incidence or latency of haematopoietic neoplasms in this study. At study termination, the final incidence of lymphomas in mice exposed to magnetic fields was 36.8% (140/380) compared with an incidence of 34.7% (66/190) in sham controls. The incidence of histiocytic sarcomas was 23.7% (90/380) in mice exposed to magnetic fields versus 22.1% (42/190) in sham controls, yielding a total incidence of haematopoietic neoplasia of 56.3% (107/190) in sham controls versus a total incidence of 59.2% (225/380) in the group exposed to circularly polarized magnetic fields. No statistically significant differences were observed (Babbitt *et al.*, 2000). In addition to the investigation of the effects of magnetic fields on haematopoietic tumours, a post-hoc histopathological analysis of brain tissues from animals in this study was performed to investigate the possibility that magnetic fields are a causative agent for primary brain tumours. Consistent with the results for haematopoietic neoplasms, histopathological examination of brains from this study provided no support for the hypothesis that exposure to magnetic fields is a significant risk factor for induction of brain tumour since no brain tumours were identified in any of the three groups described above (Kharazi *et al*., 1999). [The Working Group noted that the primary strengths of this study are that it evaluated the potential carcinogenicity of a previously unstudied type of exposure (circularly polarized rather than linearly polarized magnetic fields), and used very large experimental groups thus increasing its statistical power and its ability to identify effects of modest magnitude.]

Using a unique study design in which three consecutive generations of CFW mice were exposed to extremely high flux densities (25 mT) of 60-Hz magnetic fields, an increased incidence of malignant lymphoma in the second (no statistical analysis given) and third generations (2/41 versus 37/92; $p < 0.001$) of exposed animals was reported (Fam & Mikhail, 1996). [The Working Group noted several deficiencies in the design and conduct of this experiment. These include small and variable group sizes, a very small number of observed malignant lesions in the F_2 generation and weaknesses in exposure assessment. Of particular concern is the inadequate control of environmental factors, including the heat, noise and vibration generated by the exposure system, and the noise and vibration made by the ventilation equipment. Because non-specific stressors have been demonstrated to increase the growth of transplantable lymphomas and other tumours in mice and to decrease survival in several other animal models, inadequate control of environmental conditions may confound the study results. These possible confounders render this study difficult to interpret.]

3.1.2 *Rat*

Groups of 100 male and 100 female Fischer 344 rats, six to seven weeks of age, were exposed for 18.5 h per day for two years to linearly polarized 60-Hz magnetic fields that were nearly pure, transient–free and had less than 3% total harmonic distortion. Groups of animals were continuously exposed to field strengths of 2 μT, 200 μT or 1000 μT, or were intermittently exposed (1 h on/1 h off) to a field strength of 1000 μT. Parallel sham control groups were housed within an identical exposure array, but were exposed to low ambient magnetic fields. The exposure system has been described by Gauger *et al.* (1999). The design of these studies allowed for continuous monitoring of magnetic field strength and waveform throughout the two-year exposure period. At termination, all animals received a full necropsy and complete histopathological evaluations were performed on all gross lesions collected from all study animals, in addition to examinations of 45 tissues per animal in all study groups. Body weight and survival were comparable in all groups. Significant differences from tumour incidences in controls observed in this study included a statistically significant decrease (50/100 in controls versus 36/100; $p < 0.045$) in the incidence of leukaemia in male rats exposed intermittently to field strengths of 1000 μT, a statistically significant increase in the incidence of preputial gland carcinomas in male rats exposed to magnetic field strengths of 200 μT (but not to 1000 μT) (0/100 in controls versus 5/100; $p = 0.032$), a statistically significant increase in the incidence of trichoepitheliomas of the skin in male rats exposed continuously to 1000 μT (0/100 in controls versus 5/100; $p = 0.029$), a statistically significant decrease in the incidence of adenomas of the adrenal cortex in female rats exposed intermittently to 1000 μT (6/100 in controls versus 0/100; $p = 0.02$), and statistically significant increases in the incidence of thyroid C-cell tumours (adenomas + carcinomas) in male rats exposed to field strengths of 2 μT (16/99 in controls versus 31/100; $p = 0.005$) and 200 μT (16/99 in controls versus 30/100; $p = 0.009$). There was also a marginal increase in thyroid C-cell tumours in male rats exposed to a continuous field strength of 1000 μT (16/99 in controls versus 25/100; $p = 0.055$), but no increase in animals intermittently exposed to 1000 μT (16/99 in controls versus 22/100; $p = 0.147$). In male rats, there was also a statistically significant increase in thyroid C-cell carcinomas at 2 μT (1/99 in controls versus 7/100; $p = 0.03$) and a non-significant increase in this rare tumour in animals intermittently exposed to 1000 μT (1/99 in controls versus 5/100; $p = 0.1$) (Boorman *et al.*, 1999a; National Toxicology Program, 1999a). [An examination by the Working Group of the historical controls used by the National Toxicology Program for the 10 most recent bioassays conducted using an identical diet (NTP-2000 diet) showed a historical incidence for thyroid C-cell tumours of 17% (102/603) with a range from 2% (1/50) to 28% (14/50), indicating no discernible problem with the controls for this tumour in this study. In the same historical database, the incidence of thyroid C-cell carcinomas is 1.7% (10/603) varying from 0% (0/50) observed for four of the 10 control datasets to 4% observed for two of the datasets (2/50 and 4/100).] The original authors (Boorman

et al., 1999a) concluded [without the benefit of adequate historical controls] that their finding was equivocal and the peer-review committee of the National Toxicology Program (1999a) reached the same conclusion. [The Working Group noted that the lack of a dose–response relationship and the as yet unknown mechanism of thyroid C-cell carcinogenesis prevent a clear interpretation of this finding. For these reasons, because the results cannot be interpreted as clearly negative and because the data are insufficient to be listed as clearly positive, the Working Group concluded that the evaluation should remain equivocal.]

In another study, groups of gestating Fischer 344 rats were exposed to similar, linearly polarized 60-Hz magnetic fields at field strengths of 2 μT, 20 μT, 200 μT and 2000 μT for 20 h per day from day 20 of gestation. At weaning, groups of 50 female offspring were exposed to the same intensities and magnetic fields as the dams had been for 20 h per day for two years. The experimental design included a group of 50 female rats as cage controls and 50 female sham-exposed controls. During the lifetime of the animals, the study was conducted using a blinded design in which investigators were unaware of group identities. Toxicological end-points included a standard battery of evaluations of the living animals, followed after death by the histopathological evaluation of gross lesions and 50 tissues per animal. The authors noted no statistically significant increases in the incidence of any tumour at any site evaluated (Mandeville *et al*., 1997). [The Working Group noted that this study included exposure during the perinatal and juvenile periods, and its design addressed the possibility of enhanced sensitivity of younger animals to the effects of magnetic fields. The blinded design of the bioassay precluded any possible influence of investigator bias on study results.]

In a third chronic bioassay in rats, groups of 48 male and 48 female Fischer 344 rats, five weeks of age, were exposed for an average of 22.6 h per day to 50-Hz magnetic fields at strengths of 500 μT or 5000 μT for two years; control groups of 48 males and 48 females received sham exposure for the same period. At termination of the study, all animals received a complete necropsy. Histopathological evaluations were performed on all gross lesions, and on all sites suspected of tumoral lesions. Survival was comparable in all study groups, and differential white blood cell counts performed after 52, 78 and 104 weeks of exposure failed to identify any effects of exposure to magnetic fields. The authors reported that exposure to magnetic fields had no effect on survival of animals of either sex or on the total incidence or number of neoplasms. The only histopathological findings that were statistically significant were an increase in the incidence of a benign lesion (fibroma) in the subcutis of male rats exposed to field strengths of 5000 μT (2/48 in controls versus 9/48; $p < 0.05$) and a decrease in the total incidence of invasive neoplasms in male rats in the group exposed to 500 μT (6/48 in controls versus 1/48; $p < 0.05$). When compared with incidence in sham controls (8/48), no increases in the incidence of thyroid C-cell tumours (benign and malignant) were observed in male rats exposed to 500 μT (10/48) or 5000 μT (6/48). The incidence of thyroid C-cell carcinomas was less than 2% in all groups.

Although the increased incidence of fibromas in male rats exposed to 5000 μT was statistically significant when compared with concurrent male sham controls, the incidence of lesions was stated to be comparable to that observed in historical controls in the same laboratory [range not given]. On this basis, the authors concluded that the increase in fibroma incidence observed in rats exposed to 5000 μT was not exposure-related. Because no differences in the incidence of metastatic neoplasms were seen in the study, the observed decrease in the incidence of invasive malignancy appears to be without biological significance (Yasui *et al.*, 1997). [The Working Group noted that this study provided only limited information because of the incomplete histopathological evaluation. Because thyroid C-cell carcinomas frequently involve the entire lobe of the thyroid gland in Fischer rats, this level of histopathological evaluation should be adequate for this tumour. However, since thyroid C-cell adenomas are generally small and difficult to separate from hyperplasia, this evaluation cannot be easily compared with the National Toxicology Program (1999a) study.]

3.2 Exposure in association with known carcinogens

3.2.1 *Multistage studies of mammary cancer*

A number of studies have investigated the effect of exposure to magnetic fields on the incidence of mammary cancer in rodents. All of these have been multistage studies in which female rats were treated with a chemical carcinogen, *N*-methyl-*N*-nitrosourea (MNU) or 7,12-dimethylbenz[*a*]anthracene (DMBA), followed by exposure to magnetic fields of different strengths and for different time intervals.

(*a*) *Multistage studies with* N-*methyl*-N-*nitrosourea*

Groups of 50 female outbred rats (obtained from the Oncology Research Center, Republic of Georgia) between 55 and 60 days of age, were intravenously injected with 50 mg/kg bw MNU. Starting two days after this treatment, the animals were exposed to a 50-Hz, 20-μT magnetic field daily for 0.5 h (group 1) or 3 h (group 2), or to a 20-μT static magnetic field, daily for 0.5 h (group 3) or 3 h (group 4). A fifth group received MNU only. Four control groups each of 25 rats received no MNU, but were exposed to the same magnetic fields as described above for groups 1–4. A 10th group of 50 rats received no treatment at all. The rats were followed for a period of two years after injection of the carcinogen. In comparison with a 59% (27/46) incidence of mammary tumours in rats receiving MNU only, a significant increase was observed in the groups exposed daily for 3 h to a 50-Hz magnetic field (93%, 43/46; $p < 0.05$) or to a static magnetic field (87%, 39/45; $p < 0.05$). These increases were not seen in rats exposed to a 50-Hz field or a static field for 0.5 h per day. In comparison with a 0% (0/48) incidence of mammary tumours in rats that received no MNU and no exposure to magnetic fields, a statistically significant increase was observed ($p < 0.05$) in the incidence of mammary tumours in non-MNU-treated rats exposed for 3 h per day to a

50-Hz magnetic field (30%, 7/23) [$p < 0.01$; χ^2 test]. The authors also noted that exposure to either type of magnetic field for 3 h per day shortened the latent period of tumour development [no statistical analysis given] and led to a change in the morphological spectrum of the mammary tumours, with more adenocarcinomas than fibroadenomas (Beniashvili *et al*., 1991).

Groups of 40 outbred female rats (obtained from the Oncology Research Center, Republic of Georgia), one month of age, were kept on a 12-h/12-h light–dark cycle, and intravenously injected with MNU (50 mg/kg bw) three times per week. Starting two days after the first dose of MNU, the animals were exposed daily for 3 h to either a 20-μT static magnetic field or a 50-Hz, 20-μT magnetic field. A group of 30 rats received MNU only. Mammary adenocarcinomas were found in 7/22 (32%) of the MNU-treated controls and in 12/30 (40%) and 15/33 (45%) of the animals exposed to the static and 50-Hz magnetic fields, respectively. These differences were not statistically significant. The mean latent period for development of mammary tumours was significantly decreased ($p < 0.05$) in the rats exposed to the 50-Hz fields (125 ± 7 days), but not to the static fields (162 ± 11 days), compared with the latent period observed in the MNU-treated controls (166 ± 4 days). In the same series of studies, experiments were carried out with animals that were kept in constant darkness or in constant light. Incidences of mammary tumours decreased to 1/38 (2.6%), 1/48 (2.1%) and 2/45 (4.4%), respectively, for the MNU, MNU plus static field and MNU plus 50-Hz field groups that had been kept in the dark. Conversely, under conditions of constant light, the tumour incidences were increased: 20/35 (57%), 25/41 (61%) and 34/42 (81%), respectively, for the three groups (Beniashvili *et al.*, 1993; Anisimov *et al.*, 1996).

(*b*) *Multistage studies with 7,12-dimethylbenz*[a]*anthracene*

The results of these studies are summarized in Table 33.

Female Sprague-Dawley rats, 52 days of age, were given 5 mg DMBA by gavage. Administration of DMBA (5 mg by gavage) was repeated at weekly intervals up to a total dose of 20 mg/animal. Beginning immediately after the first dose of DMBA, the treatment groups were exposed 24 h per day for 13 weeks to either a static magnetic field of 15 mT (18 rats), a 50-Hz magnetic field of 30 mT (1 group of 15 and 1 group of 18 rats) or a non-uniform 50-Hz magnetic field ranging from 0.3–1 μT (36 rats). Control groups equal in size to those of the treated rats were sham-exposed. Rats were palpated weekly to assess development of mammary tumours. After 13 weeks, all rats were necropsied and the number and weight or size of the tumours were determined. The exposure system was adequately described and consisted of six identical solenoidal coils and six sham coils of the same dimensions. The DMBA-treated age-matched reference control groups were kept in a separate room (ambient field, 0.05–0.15 μT). In sham-exposed animals and reference controls, the tumour incidence varied between 50 and 78% in the different experiments. The average number of mammary tumours per tumour-bearing animal varied between 1.6 and 2.9. In none of the experiments did exposure to magnetic fields significantly alter tumour incidence

Table 33. Multistage studies of mammary cancer in female Sprague-Dawley rats treated with 7,12-dimethylbenz[*a*]anthracene (4 weekly gavage doses of 5 mg/animal, unless otherwise stated) and exposed to magnetic fields for 13 weeks (unless otherwise indicated)

Reference	Exposure conditions	Exposure and control groups (no. of animals)	No. of animals with tumours	Tumour incidence (%)	Total no. of tumours	No. of tumours per tumour-bearing animal	Remarks
Mevissen *et al.* (1993)	15 mT, static	Exposed (18)	10	56	17	1.7 ± 0.31	
		Sham-exposed (18)	14	78	30	2.1 ± 0.28	
		Reference control (8)	6	75	16	2.7 ± 0.35	
	30 mT, 50 Hz	Exposed (18)	14	78	40	2.8 ± 0.63 *	* $p < 0.05$ compared with sham-exposed animals
		Sham-exposed (18)	10	56	22	2.2 ± 0.47	
		Reference control (18)	12	67	20	1.7 ± 0.23	
	30 mT, 50 Hz	Exposed (15)	6	40	11	1.8 ± 0.34	
		Sham-exposed (18)	9	50	14	1.6 ± 0.17	
		Reference control (9)	5	55	12	2.4 ± 0.37	
	0.3–1 μT, 50 Hz	Exposed (36)	21	58	47	2.2 ± 0.3	
		Sham-exposed (36)	21	58	60	2.9 ± 0.45	
Löscher *et al.* (1993)	100 μT, 50 Hz	Exposed (99)	51	52 *	82	~ 1.6	All figures calculated from curves
		Sham-exposed (99)	34	34	62	~ 1.8	* $p < 0.05$ compared with sham-exposed animals
Baum *et al.* (1995)[a]	100 μT, 50 Hz	Exposed (99)	65	66	134	~ 2.1	No. of animals with adenocarcinoma: exposed, 62; sham-exposed, 49 ($p < 0.05$)
		Sham-exposed (99)	57	58	113	~ 2.0	
		Exposed, no DMBA (9)	0	0	–	–	
		Sham-exposed, no DMBA (9)	0	0	–	–	Tumour volume in exposed animals significantly larger than in sham-exposed animals ($p < 0.05$)
Löscher *et al.* (1994)	0.3–1 μT, 50 Hz	Exposed (36)	24	67	77	3.2 ± 0.54	
		Sham-exposed (36)	22	61	95	4.3 ± 0.83	

Table 33 (contd)

Reference	Exposure conditions	Exposure and control groups (no. of animals)	No. of animals with tumours	Tumour incidence (%)	Total no. of tumours	No. of tumours per tumour-bearing animal	Remarks
Mevissen *et al*. (1996a)	10 μT, 50 Hz	Exposed (99) Sham-exposed (99) Exposed, no DMBA (9) Sham-exposed, no DMBA (9)	66 60 0 0	67 61 0 0	151 129 – –	~ 2.5 ~ 2.5 – –	
Mevissen *et al*. (1996b)	50 μT, 50 Hz	Exposed (99) Sham-exposed (99) Exposed, no DMBA (9) Sham-exposed, no DMBA (9)	69 55 0 0	70 * 56 0 0	193 139 – –	~ 2.7 ~ 2.5 – –	* $p < 0.05$ compared with sham-exposed animals
Mevissen *et al*. (1998a)	100 μT, 50 Hz	Exposed (99) Sham-exposed (99)	83 62	84 * 63	297 230	~ 3.8 ~ 3.8	* $p < 0.05$ compared with sham-exposed animals
Ekström *et al*. (1998)	250 μT, 50 Hz 500 μT, 50 Hz	Exposed (60) Exposed (60) Sham-exposed (60)	42 42 43	70 70 72	102 90 111	2.4 2.1 2.6	A single intragastric dose (7 mg/animal) of DMBA was given one week before exposure to the magnetic field for 21 weeks, 15 s on/15s off
Anderson *et al*. (1999); National Toxicology Program (1999b)	100 μT, 50 Hz 500 μT, 50 Hz 100 μT, 60 Hz	Exposed (100) Exposed (100) Exposed (100) Sham-exposed (100)	86 96 96 92	86 (carc.) 96 96 92	528 * (carc.) 561 692 691	5.3 ± 4.4 * 6.5 ± 4.9 6.9 ± 4.8 6.9 ± 4.8	* $p < 0.05$, decrease

Table 33 (contd)

Reference	Exposure conditions	Exposure and control groups (no. of animals)	No. of animals with tumours	Tumour incidence (%)	Total no. of tumours	No. of tumours per tumour bearing animal	Remarks
Anderson *et al.* (1999); National Toxicology Program (1999b)	100 µT, 50 Hz 500 µT, 50 Hz	Exposed (100) Exposed (100) Sham-exposed (100)	48 38 43	48 (carc.) 38 43	90 (carc.) 79 102	0.9 ± 1.3 0.8 ± 1.3 1.0 ± 1.9	DMBA-treatment with 4 × 2 mg/ animal at weekly intervals
Boorman *et al.* (1999b); National Toxicology Program (1999b)	100 µT, 50 Hz 500 µT, 50 Hz 100 µT, 60 Hz	Exposed (100) Exposed (100) Exposed (100) Sham-exposed (100)	90 95 85 96	90 (carc.) 95 85 * 96	494 * (carc.) 547 433 * 649	4.9 ± 4.2 * 5.5 ± 3.9 4.3 ± 3.9 * 6.5 ± 4.8	* $p < 0.05$, decrease. A single intra-gastric dose of 10 mg/rat followed by exposure to magnetic field for 26 weeks
Thun-Battersby *et al.* (1999)	100 µT, 50 Hz	Exposed (99) Sham-exposed (99)	64 50	65 * 51	166 116	~ 2.3 ~ 2.6	* $p = 0.044$ compared with sham-exposed animals DMBA-treatment with a single oral dose (10 mg/rat), at one week after the start of exposure to magnetic field for 27 weeks

carc., carcinoma; DMBA, 7,12-dimethylbenz[*a*]anthracene

[a] This study provided histological confirmation of the results reported in Löscher *et al.* (1993).

although in one of the groups exposed to the 50-Hz magnetic field of 30 mT, the number of tumours per tumour-bearing animal was significantly increased ($p < 0.05$). This increase was not seen in the other experiment at 30 mT or in the combined analysis. Furthermore, exposure to the static magnetic field of 15 mT significantly enhanced the tumour weight. Exposure to the non-uniform magnetic field (50 Hz; 0.3–1 μT) had no significant effects on tumour multiplicity or tumour sites. The authors concluded that these experiments suggest that magnetic fields at high flux densities may act as a promoter or co-promoter of mammary cancer. However, they considered this interpretation to be tentative because of the limitations of this study, particularly the small sample size used to study exposure to a magnetic field. Confirmation would require further experiments with larger groups of animals (Mevissen *et al.*, 1993).

A group of 99 female Sprague-Dawley rats, 52 days of age, was exposed to a homogeneous 50-Hz magnetic field of 100 μT for 24 h per day for a period of 13 weeks; another group of 99 rats was sham-exposed. The exposure chambers (Merritt coils, adequately described) were identical for both groups of animals. DMBA (5 mg) was administered by gavage to both groups on the first day of exposure to the magnetic field and at weekly intervals thereafter up to a total dose of 20 mg/rat. The animals were palpated once weekly to assess the development of mammary tumours. Eight weeks after the first dose of DMBA, the incidence of palpable mammary tumours in rats exposed to the magnetic field was significantly higher than in sham-exposed animals ($p < 0.05$). This difference was observed throughout the period of exposure, at the end of which the tumour incidence in exposed rats was 52% (51/99) versus 34% (34/99) in the sham-exposed controls ($p < 0.05$). The tumour size ($p = 0.013$) and the number of tumours per animal ($p < 0.05$) were also increased in the exposed group (Löscher *et al.*, 1993). To provide histopathological confirmation, data on palpable tumours were examined separately for the study described above. Interrupted step sections were prepared from all mammary glands from all animals, yielding 50–60 sections/rat. The incidence of mammary tumours (all types) was 66% (65/99) in magnetic field-exposed and 58% (57/99) in sham-exposed rats ($p > 0.05$). The percentage of animals with mammary adenocarcinomas was significantly higher in the group exposed to DMBA plus a magnetic field than in the sham-exposed controls treated with DMBA (62/99 versus 49/99, $p < 0.05$). Forty-five other organs or tissues were also examined and no significant changes in tumour incidence were noted (Baum *et al.*, 1995).

Using the same protocol (exposure to DMBA and magnetic fields) as Löscher *et al.* (1993) with the addition of a full histopathological review, one group of 36 female Sprague-Dawley rats was exposed to a magnetic field of 0.3–1 μT at 50 Hz and a second group was sham-exposed. In this study, 67% (24/36) of the animals exposed to the magnetic field versus 61% (22/36) of the sham-exposed controls had mammary tumours ($p > 0.05$) and there were also no differences observed in the number of tumours per animal or in average tumour size (Löscher *et al.*, 1994).

Using the same experimental protocol (DMBA, magnetic fields) as Löscher *et al.* (1994), one group of 99 female Sprague-Dawley rats was exposed continuously to

50-Hz, 10-μT magnetic fields for 13 weeks and a second group of 99 rats was sham-exposed. At autopsy, 61% (60/99) of the sham-exposed and 67% (66/99) of the magnetic field-exposed rats had developed macroscopically visible mammary tumours ($p > 0.05$). The average size of the individual tumours and the average sum of all tumours per tumour-bearing rat were similar in both groups (Mevissen *et al.*, 1996a).

The experimental design described above was used to study the effects of a higher field strength of 50 μT. Within eight weeks after the first DMBA administration, the group of rats exposed to a 50-Hz, 50-μT magnetic field exhibited significantly more ($p = 0.028$) palpable mammary tumours than sham-exposed animals. Autopsy revealed significantly more ($p < 0.05$) macroscopically visible mammary tumours (69/99) in rats exposed to magnetic fields than did controls treated with DMBA alone (55/99). No differences in the numbers of tumours per tumour-bearing animal or tumour size were seen (Mevissen *et al.*, 1996b).

Löscher and Mevissen (1995) published a regression analysis of the four studies described above (Löscher *et al.*, 1993, 1994; Baum *et al.*, 1995; Mevissen *et al.*, 1996a,b) in which exposure level was compared with the percentage increase in incidence over controls of palpable mammary tumours after 13 weeks of treatment. This analysis demonstrated a highly significant ($p < 0.01$) trend.

A previous study (Löscher *et al.*, 1993; Baum *et al.*, 1995) was replicated in the same laboratory under the same experimental conditions (exposure to DMBA and a 50-Hz, 100-μT magnetic field). After nine weeks of treatment, the incidence of palpable mammary tumours in the group exposed to a magnetic field was significantly higher than that in the sham-exposed group ($p < 0.05$). This difference was maintained throughout the remainder of the period of exposure. At 13 weeks, the incidence of macroscopically visible mammary tumours was 63% (62/99) in controls and 84% (83/99) in exposed rats ($p < 0.05$). No differences were observed in the number of tumours per tumour-bearing rat or in the average tumour size. The addition of this data point to the previous regression analysis by Löscher & Mevissen (1995) did not markedly alter the significant trend ($p < 0.05$) (Mevissen *et al.*, 1998a).

In a study performed in another laboratory, female Sprague-Dawley rats, 52 days of age, were randomly allocated to one of three groups of 60 animals each. All rats received a single gavage dose of 7 mg DMBA on day 1 of the experiment. Beginning one week later, groups were exposed to intermittent (15 s on/15 s off) transient-associated 50-Hz magnetic fields at a field strength of 250 μT or 500 μT and another group was sham-exposed. The exposure treatment was continued for 24 h per day for 21 weeks, with intermissions for animal care and observations. Animals were palpated twice weekly to identify mammary tumours, but no histological analysis was carried out. The tumour incidence in the two groups exposed to the magnetic fields was 70% (42/60 in both groups), and the incidence in the DMBA-treated controls was 72% (43/60). The total numbers of tumours were 102 (250 μT exposure group), 90 (500 μT exposure group) and 111 (sham-exposed). These values were not statistically different.

Total tumour weight and total tumour volume were not statistically different between groups (Ekström *et al.*, 1998).

Groups of 100 female Sprague-Dawley rats, 50 days of age, received four weekly gavage doses of 5 mg DMBA per animal. After the first DMBA dose, exposure to ambient fields (sham exposure), 50-Hz magnetic fields (field strength of 100 or 500 μT) or 60-Hz fields (field strength of 100 μT) was initiated. The animals were exposed to magnetic or sham fields for 18.5 h per day, seven days per week for 13 weeks. In a second study, groups of 100 female Sprague-Dawley rats received lower doses of DMBA (2 mg/animal per week for four weeks). After the first dose of DMBA, rats were exposed to ambient fields (sham exposure) or 50-Hz magnetic fields at a field strength of 100 or 500 μT for 18.5 h per day, seven days per week for 13 weeks. Rats were weighed and palpated weekly for the presence of mammary tumours. Palpable mammary tumours were examined histologically. Exposure to magnetic fields had no effect on body weight gains or on the time of appearance of mammary tumours in either study. In the first study, the mammary cancer incidences were 92% (92/100), 86% (86/100), 96% (96/100) and 96% (96/100) for the DMBA-treated control, 50-Hz, 100-μT, 50-Hz, 500-μT and 60-Hz, 100-μT groups, respectively. The average numbers of mammary carcinomas per animal were 6.9, 5.3 ($p < 0.05$, decrease), 6.5 and 6.9 for the same groups, respectively. In the second study, the mammary cancer incidences were 43% (43/100), 48% (48/100) and 38% (38/100) for the DMBA-treated control, 50-Hz, 100-μT and 50-Hz, 500-μT groups, respectively. There was no effect of exposure to magnetic fields on the number of tumours per rat or tumour size (Anderson *et al.*, 1999; National Toxicology Program, 1999b). [The Working Group noted that the high tumour incidence observed in the first study effectively precluded the identification of increases in tumour incidence at the end of the study. The decrease in average number of tumours per animal exposed to magnetic fields of 100 μT coincided with a 7% decrease in survival which could have affected this finding.]

Groups of 100 female Sprague-Dawley rats, 50 days of age, received a single dose of 10 mg DMBA by gavage, followed by exposure to ambient fields (strength < 0.1 μT; sham exposure), 50-Hz magnetic fields (strength, 100 or 500 μT) or 60-Hz magnetic fields (strength, 100 μT). The animals were exposed for 18.5 h per day, seven days per week, for 26 weeks. Rats were palpated weekly for mammary tumours. After 26 weeks of exposure to magnetic fields or sham exposure, the animals were killed and the mammary tumours counted and measured; mammary tumours were confirmed histologically. Exposure to magnetic fields had no effect on body weight gain or the time of appearance of mammary tumours. The incidence of mammary cancer was 96% (96/100), 90% (90/100; $p = 0.07$)), 95% (95/100; $p = 0.52$) and 85% (85/100; $p = 0.009$) for the DMBA-treated control, 50-Hz, 100-μT, 50-Hz, 500-μT, and 60-Hz, 100-μT groups, respectively. The total numbers of carcinomas were 649, 494 ($p < 0.05$), 547 and 433 ($p < 0.05$) for the same groups, respectively. The number of fibroadenomas varied from 276 to 319 per group, with the lowest number in the 60-Hz, 100-μT exposure group. Measurement of the tumours revealed no difference in tumour size between

groups (Boorman *et al.*, 1999b; National Toxicology Program, 1999b). [The Working Group noted that the high tumour incidence observed in sham control animals effectively precluded the identification of increases in tumour incidence at the end of the study. However, unlike the first National Toxicology Program experiment (Anderson *et al.*, 1999; National Toxicology Program, 1999b), the decreases in average number of tumours per animal were probably not associated with differences in survival.]

Using the protocol of Mevissen *et al.* (1998b) the treatment period was extended to 27 weeks. Groups of 99 female Sprague-Dawley rats, 45–49 days of age, were exposed either to sham fields or to 50-Hz, 100-μT magnetic fields for 24 h per day, seven days per week. A single dose of 10 mg DMBA/rat by gavage was administered one week after study start to both sham-exposed rats and those exposed to magnetic fields (rather than four weekly doses of 5 mg). The animals were palpated once weekly from week 6 onwards to assess the development of mammary tumours. The incidence of palpable mammary tumours in the group exposed to DMBA plus magnetic fields was increased by week 13 ($p = 0.029$) and continued to be elevated throughout the study in comparison with the incidence in the DMBA-treated, sham-exposed group. At study termination, the incidence of histologically verified mammary tumours was 50.5% (50/99) in controls and 64.7% (64/99) in exposed rats, the difference being statistically significant ($p = 0.044$). The incidence of adenocarcinomas was not significantly different between the two groups (42.4%, 42/99 in controls versus 52.5%, 52/99 in exposed rats). When tumour incidence was evaluated separately for each of the six mammary complexes, the most pronounced effect of exposure to the magnetic field was seen in the L/R1 glands, where the overall tumour incidences were 18.2% (18/99) and 30.3% (30/99) for control and exposed rats, respectively ($p < 0.05$). No differences in the size of mammary tumours or number of tumours per animal were noted (Thun-Battersby *et al.*, 1999). [The Working Group questioned the feasibility of attributing the site of origin of a mammary tumour to a specific mammary gland, but agreed that increases in L/R1-3 as a complex appear to be exposure-related.]

3.2.2 *Multistage studies of skin cancer*

(*a*) *Mouse (conventional)*

Groups of 32 female SENCAR mice, six to seven weeks of age, were sham-exposed or exposed to 60-Hz, 2000-μT continuous magnetic fields (Merritt exposure system described in Stuchly *et al.* (1991) [geomagnetic field not given]) for 6 h per day, five days per week for 21 weeks with or without weekly co-promotion with 1 μg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) [four groups in total]. All animals received a single topical initiation with DMBA on the dorsal skin at a dose of 10 nmol (2.56 μg) dissolved in 200 μL acetone one week prior to exposure to the magnetic field. Any macroscopically visible tumours and other tissue abnormalities such as enlarged spleens and lymph nodes were examined histopathologically. [Minimum size of papillomas was not reported.] The development of papillomas in the magnetic field-exposed mice treated

with TPA was no earlier than in sham-exposed animals treated with TPA ($p = 0.898$). At termination of the experiment, the total number of animals with papillomas was 28/31 in the sham-exposed group treated with TPA versus 29/32 animals in the matching group of animals exposed to the magnetic field. The average number of papillomas per tumour-bearing animal was 10 in both sham-exposed and magnetic field-exposed animals treated with TPA. All lesions were benign but two mice from the group exposed to the magnetic field and treated with TPA were found to have one papilloma each with very mild invasion of the squamous epithelium and another mouse was diagnosed as having a lymphoma. The investigators concluded that exposure to a magnetic field did not act as a promoter since none of the DMBA-initiated mice developed papillomas in the absence of treatment with TPA regardless whether or not they were exposed to a magnetic field. A positive control group (21 mice that received 2 μg TPA twice a week) showed no increase in tumour incidence compared with the control group (mice that received 1 μg TPA once a week) [*p*-value not given]; the author suggested a saturation of the system allowing no opportunity to detect a co-promotional effect (McLean *et al*., 1991).

In a second study, two groups of 48 female SENCAR mice, six weeks of age, were sham-exposed or exposed to a 60-Hz, 2000-μT magnetic field (Merritt exposure system described in Stuchly *et al*. (1991)) for 23 weeks; all animals received a weekly application of 0.3 μg TPA. All animals received a single topical initiation with DMBA (10 nmol dissolved in 200 μL acetone) on the dorsal skin one week prior to exposure to the magnetic field. An increased rate of papilloma development in animals exposed to magnetic fields compared with the sham-exposed controls was reported to be significant at weeks 16 ($p = 0.01$, Fisher exact test), 17 ($p = 0.02$) and 18 ($p = 0.02$), but was not significant at the end of the study ($p = 0.16$). The number of tumours per animal was not statistically different from the controls at the end of the study ($p = 0.21$, Wilcoxon test), but a significant difference was also reported at weeks 16 ($p = 0.01$), 17 ($p = 0.03$) and 18 ($p = 0.03$) (Stuchly *et al.*, 1992). [The authors did not report any significant tests on papillomas per tumour-bearing animal although it is clear that the average number of tumours per tumour-bearing animal was lower than that seen in the first study of MacLean *et al.* (1991)]. The same study was prolonged to 52 weeks; TPA treatment was discontinued after week 24. The authors reported no overall increase in total tumours or papillomas alone in animals exposed to magnetic fields, but more animals exposed to magnetic fields developed squamous-cell carcinoma (8/48) than did sham-exposed animals (1/48) [$p < 0.03$, Fisher exact test two-sided]. [The number of tumours per animal was not reported.] The conclusion of the authors was that exposure to magnetic fields may accelerate progression to malignancy (McLean *et al*., 1995).

Two further studies replicating the 23-week study described by Stuchly *et al*. (1992) and using the same experimental design were performed. Two groups of 47 or 48 female SENCAR mice were used in each replicate. At week 23, tumour incidence in the first replicate was identical in animals exposed to a 2000-μT magnetic field and sham-exposed controls. In the second replicate, tumour incidence in mice exposed to

a 2000-μT magnetic field was significantly reduced compared to the incidence in sham-exposed controls ($p = 0.04$, Fisher's exact test). The total number of tumours seen by Stuchly *et al*. (1992) was higher in the group exposed to the magnetic field (86) than in the sham-exposed group (48) ($p = 0.15$), whereas the opposite effect was seen in the two replicates (33 in the group exposed to the magnetic field versus 50 in the sham-exposed group [$p = 0.26$] and 27 in the group exposed to the magnetic field versus 86 in the sham-exposed group [$p = 0.01$]). The study does not support a role for exposure to a magnetic field as a strong co-promoter in the mouse skin-tumour model (McLean *et al*., 1997).

In another study of skin tumour promotion, groups of 30 female NMRI/HAN mice, seven weeks old, initiated with 25.6 μg DMBA in 200 μL acetone on the shaved dorsal skin or uninitiated (acetone only), were exposed to a 50-Hz magnetic field of strength of 50 or 500 μT or to sham-exposure conditions for 19 h per day on weekdays and for 21 h per day during weekends for a period of 104 weeks [six groups in total]. The exposure system has been described by Rannug *et al.* (1993a). In addition, TPA (given topically at a dose of 3.08 μg in 200 μL acetone twice per week), was used as a positive control in groups treated with either acetone alone or DMBA in acetone. The detection limit for the size of papilloma was 2 mm. After 104 weeks, the animals were assessed by complete necropsy and histopathological evaluation of skin tumour types. The survival of uninitiated mice exposed to the 500-μT magnetic field was significantly reduced in comparison to uninitiated controls ($p = 0.029$; 10% versus 23.3%). Exposure to the magnetic field had no significant effect on survival in any other group. Skin samples taken from members of each group at different times and analysed for hyperplasia showed a hyperplastic response in animals treated with DMBA plus TPA and those treated with TPA alone; no increased hyperplastic response was observed in any of the groups exposed to the magnetic field. No skin tumours were found in uninitiated mice in either the sham-exposed group or the group exposed to the magnetic field but one uninitiated TPA-treated animal had two skin tumours. No statistically significant differences in the number of animals with skin tumours or in the total number of skin tumours were reported in the initiated animals. The authors concluded that exposure to magnetic fields did not promote skin tumour incidence, nor act as a complete skin carcinogen. Full necropsy at death showed no significant change in incidence of other tumours associated with exposure to magnetic fields (Rannug *et al*., 1993b).

In a second study in female SENCAR mice, the tumour-promoting effects of continuous and intermittent exposure to 50-Hz magnetic fields for up to 105 weeks were examined. Starting one week after initiation with 2.56 μg DMBA in 200 μL acetone, groups of 40 mice were exposed to continuous magnetic fields at strengths of 50 or 500 μT or to intermittent fields (15 s on/15 s off) at the same field strengths. Untreated (acetone), sham-treated (DMBA alone) and TPA-treated (initiated and uninitiated) groups were also included. No skin tumours were reported in animals treated with DMBA and then exposed to continuous magnetic fields at either 50 μT or 500 μT. Four skin tumours were found in 4/40 animals in the group intermittently exposed to a field

strength of 50 μT and 13 skin tumours were found in 5/40 animals animals in the group intermittently exposed to 500 μT compared with two skin tumours in 2/40 DMBA-treated sham-exposed animals. These increases were not significantly different when the two intermittently exposed groups were combined and compared with the sham-exposed group [*p*-value not given], but a significant difference was obtained when combined comparisons of continuous versus intermittent exposure were performed [$p = 0.014$, analysis according to Peto (1974)]. [The Working Group noted that it is not clear whether the pooling of data across groups is appropriate.] Similar findings were reported for the total number of skin tumours [no significant difference except when the pooled continuous exposure group was compared to the pooled intermittent exposure group; $p < 0.01$.] A linear regression analysis comparing the cumulative number of skin tumours in skin tumour-bearing animals exposed intermittently to different field strengths with the DMBA-treated controls gave a one-sided *p*-value of 0.045 which the authors noted as suggesting a dose dependency. No hyperplastic response was reported in animals exposed to magnetic fields. Histopathological investigation showed that carcinomas (squamous, spindle or basal) occurred in both the intermittently exposed groups and in the positive control group (DMBA plus TPA), but not in the DMBA-treated control group (where both lesions observed were papillomas). The investigators concluded that intermittent exposure could be weakly promoting, but interpretation is uncertain because of the possibility of induced electric fields due to mechanical switching and associated occurrence of transients (Rannug *et al.*, 1994).

Groups of 56 female SENCAR mice, four to six weeks of age, were initiated with 10 nmol DMBA in 200 μL acetone before being exposed to ambient magnetic fields (mean field strength, 0.11 μT) or continuous magnetic fields of 2000 μT, 60 Hz for 23 weeks. Exposure to magnetic fields was combined with topical application of TPA once a week at doses of 0 (acetone only), 0.85 nmol (1.04 μg), 1.7 nmol (2 μg) or 3.4 nmol (4.2 μg) [a total of eight groups]. An additional group of 40 uninitiated mice was given a weekly dose of 3.4 nmol (4.2 μg) TPA and exposed to an ambient-strength magnetic field. The incidence of skin lesions [minimum size of tumour detected was not reported] was monitored and tumours were histologically evaluated at the end of the study. Tumour incidence [reported only as plots] did not differ between animals exposed to magnetic fields and ambient controls. [The Working Group noted that data on tumour multiplicity, total tumours, time to first tumour and survival of animals were not reported although some were shown in the figures, and *p*-values were given for comparisons of tumour multiplicity and incidence. The Working Group also noted several inconsistencies between the *p*-values and data reported; for example, a *p*-value of 0.32 was given in the Table for the group in which 3.4 (4.2 μg) nmol TPA was used as a promoter compared with the ambient control but a Figure illustrating the same results reported that 55/56 animals in the ambient group had tumours and that 56/56 animals in the group exposed to magnetic fields developed tumours. It was also noted that many of the *p*-values were repeated in both tumour incidence and tumour multiplicity tables.] The conclusion of the authors was that, within the sensitivity limits of

this animal model and the exposure parameters employed, no promotional or co-promotional effects of exposure to a 2-mT magnetic field were observed in the two-stage skin cancer model (Sasser *et al*., 1998).

(*b*) *Mouse (genetically modified)*

Groups of 21–22 female mice of a transgenic hybrid strain (K2) that overexpresses the human ornithine decarboxylase gene and groups of 21–22 female non-transgenic littermates, seven to nine months of age, were exposed to ultraviolet light (200 J/m^2, 35 min/day, three times per week) for 10.5 months in order to induce skin cancer. The investigation of possible promotional or co-promotional effects of ELF magnetic fields was performed in groups of sham-exposed mice and mice exposed for 24 h to intermittent magnetic fields (field strengths of 1.3, 13 and 130 μT, each applied in succession for 20 min, followed by a 2-h pause) or continuous magnetic fields (50 Hz, 100 μT). The field generator used for this study was well described. Skin tumour incidence and tumour multiplicity were monitored, and the tumours were histologically evaluated at the end of the study. An increase in the rate of onset of macroscopically detectable tumours, with a minimum size of 2 mm, was reported in both transgenic and non-transgenic animals exposed to magnetic fields. This effect was statistically significant in the combined analysis, i.e. when all animals exposed to a magnetic field were compared with all controls ($p < 0.015$), and also when transgenic animals exposed to intermittent and continuous magnetic fields were compared to the ultraviolet light-treated controls ($p < 0.025$), but this effect was not significant in non-transgenic mice ($p < 0.15$). No significant differences were seen in the individual comparisons between the separate groups exposed to a magnetic field and the controls. Measurements of human ornithine decarboxylase activity did not show any significant changes as a function of exposure to magnetic fields ($p < 0.10$). The authors concluded that exposure to magnetic fields accelerated tumour growth (Kumlin *et al*., 1998a). [The Working Group considered that the evaluation of these findings is difficult for two reasons. Firstly, a new skin cancer model using transgenic mice was used, but the investigators did not include a positive control, which would have been helpful in the interpretation of the findings, and, secondly, the results on tumour incidence as a function of time were presented only as values summed over the groups continuously and intermittently exposed to magnetic fields.]

3.2.3 *Multistage studies of liver cancer*

(*a*) *Mouse*

Groups of 50 female CBA/S mice, 3–5 weeks of age, were exposed to ionizing radiation (using a 4- or 6-MV linear accelerator). The total body dose was 4 Gy delivered as three equal fractions of 1.33 Gy at one-week intervals. Simultaneously, the animals were exposed either to a 50-Hz vertical magnetic field of field strength 1.26, 12.6 and 126 μT (each applied in succession for 20 min) or were sham-exposed. A third group

served as cage controls. The mice were exposed to the magnetic field or sham-exposed for 24 h per day for 1.5 years. An increase in the incidence of basophilic liver foci in mice exposed to magnetic fields was statistically significant when compared to sham-exposed mice ($p = 0.002$; Poly-3 test). The incidence of liver carcinomas showed a slight, but not statistically significant ($p = 0.147$) increase in the mice exposed to a magnetic field (14/48, 28%) compared to the sham-exposed group (7/50, 14%) (Heikkinen *et al*., 2001).

(*b*) *Rat*

Two studies in rats have been conducted to evaluate the possible tumour promoting and/or co-promoting effects of a 50-Hz magnetic field on chemically initiated liver tumours. The rat liver foci assay was used for the experiments (Rannug *et al*., 1993b,c). Preneoplastic lesions were initiated in male Sprague-Dawley rats weighing approximately 200 g [age not specified] by intraperitoneal administration of 30 mg/kg bw *N*-nitrosodiethylamine (NDEA) 24 h after a 70% partial hepatectomy. These studies reported the number, the volume percentage and the mean area of altered hepatic foci in the liver, as determined by use of two enzyme markers, the placental glutathione-S-transferase (GST-P) and γ-glutamyltranspeptidase (γGT). Markers were measured by immunohistochemical methods using sections from the right lateral lobe of the liver.

In the first study, rats were exposed to either a 50-Hz magnetic field (4 groups of 10 rats) or to phenobarbital (2 groups of 10 rats) given in the diet at a concentration of 300 ppm for 12 weeks, beginning one week after administration of NDEA. Two separate experiments were conducted. In the first experiment, the flux densities to which the animals were exposed were 0.5 and 50 μT and for the second experiment 5 and 500 μT were used. The fields were switched on for 19–21 h per day, seven days per week. The exposure system is described in Rannug *et al*. (1993a). The experiments were performed in a blind fashion and sham controls (2 groups of 10 rats) were used as matching controls. The body weight gains and liver weights did not differ between animals exposed to magnetic fields and controls whereas the liver weight was significantly increased in rats used as positive controls (phenobarbital). The number of γGT-positive foci per cm^2, the mean focus area ($cm^2 \times 10^{-4}$) and the number of foci per cm^3 in groups exposed to magnetic fields did not differ significantly from the number seen in the controls. A significant difference was seen when the positive control (NDEA + phenobarbital) was compared to the control rats (NDEA) ($p < 0.01$). A significant increase in the percentage volume occupied by γGT-positive foci was observed at a field strength of 50 μT compared with the control rats ($p < 0.05$). In the second experiment, no such increase in γGT-positive foci was seen in association with exposure to magnetic fields. However, the percentage volume occupied by foci was lower in the first experiment (experiment 1: NDEA, 0.002 ± 0.001; experiment 2: NDEA, 0.006 ± 0.003), and the magnitude was similar to that seen in the first experiment in animals treated with NDEA and exposed to a magnetic field of 0.5 μT (0.005 ± 0.002) and in animals treated with NDEA and exposed to a magnetic field of

50 μT (0.005 ± 0.001). No effects on GST-P-positive foci were observed for any parameters measured in either experiment when compared with the NDEA control (Rannug *et al*., 1993c).

A second study, undertaken to investigate the possible interaction between exposure to a 50-Hz magnetic field, partial hepatectomy, initiation with NDEA and promotion with phenobarbital, was performed as described above, but the exposure to a magnetic field began immediately after partial hepatectomy. Four groups (9–10 rats each) were included in the study and treated as follows: one group was treated with NDEA alone, one group with NDEA followed by phenobarbital and two groups were given NDEA and phenobarbital and were exposed to 50-Hz magnetic fields, at field strengths of 0.5 and 500 μT. No effects on the liver:body weight ratio or body weight gain in the treated animals were observed after the 12-week exposure period when compared with controls. In the group exposed to magnetic fields of 0.5 μT, the number of γGT-positive foci per cm^3 (931 ± 131) was significantly decreased compared with the matching control group (1413 ± 181) ($p < 0.05$), and a reduction in GST-P-positive foci was associated with the higher field strength (500 μT) for the mean focus area and the percentage volume occupied by foci ($p < 0.05$) (Rannug *et al*., 1993a).

3.2.4 *Multistage studies of leukaemia or lymphoma*

(*a*) *Mouse (conventional)*

Groups of female CBA/S mice, 25 ± 5 days of age, were exposed either to X-rays (four fractions of 1.31 Gy at a dose rate of 0.45 Gy/min at four-day intervals; 64 mice in total), to pulsed magnetic field (vertical 20-kHz field with a field strength of 15 μT; 53 mice in total) for the lifetime of the animal or to both X-rays and pulsed magnetic field (exposure to magnetic field started immediately after each X-ray exposure; 63 mice in total) or received no treatment (stray-field, field strength < 0.7 μT; 47 mice in total). The mice were killed when moribund and autopsied; haemoglobin concentration, leukocyte counts and differential leukocyte counts were determined and 10 tissues were examined histologically. The diagnosis of lymphoma by microscopy was confined to thymic and non-thymic types. The difference in mean survival time between mice exposed to X-rays alone versus those exposed to both X-rays and magnetic field was not significant. However, mean survival time in mice exposed to magnetic field alone was significantly reduced in comparison to untreated controls ($p = 0.002$). Lymphoma incidence was increased in animals exposed to X-rays; however exposure to magnetic fields had no effect: the incidence of lymphomas was 42/64 (65.6%) in mice exposed to X-rays alone, 45/63 (71.4%) in mice exposed to both X-rays and magnetic field, 3/53 (5.7%) in mice exposed to magnetic field alone and 3/47 (6.4%) in untreated controls. The body weights of mice exposed to X-rays alone or both X-rays and magnetic field were not significantly different from those of controls, but the body weights of mice exposed to magnetic field alone were significantly greater than those of controls. Under the environmental conditions used, pulsed magnetic fields did not affect the frequency of spontaneous

lymphoma, or the frequency of lymphomas induced by exposure to X-rays (Svedenstål & Holmberg, 1993). [The Working Group noted that animals were introduced to the experimental conditions at different time points, in some cases over a period of nearly one year.]

Groups of newborn Swiss Webster mice were subcutaneously injected with 0 or 35 μg DMBA in 1% gelatin, and, two weeks later, exposed to a 50-Hz magnetic field at field strength of 1 mT for 3 h per day, six days a week for 16 weeks, or were sham-exposed. All surviving mice were killed and autopsied at 32 weeks of age. No thymic lymphoma/leukaemia was found in the 84 sham-exposed mice that received 1% gelatin alone. There was no significant difference in survival times. The incidences of pre-malignant changes in thymus, early thymic lymphoma and advanced lymphoma were: sham-exposed males treated with DMBA, 18/80 (22.5%); males exposed to a magnetic field and treated with DMBA, 24/89 (27.0%); sham-exposed females treated with DMBA, 28/75 (37.3%); and females exposed to a magnetic field and treated with DMBA, 26/76 (34.2%); and demonstrated no statistically significant differences within a sex. The incidence of 'dense' metastatic infiltrations in the livers of the mice treated with DMBA and exposure to a magnetic field was significantly greater ($p < 0.01$) than that in the sham-exposed group treated with DMBA. The number of granulocytic leukaemia-bearing mice in the former group was 5/165 and that in the latter group was 4/155. The authors concluded that the study had found no evidence for a 'striking promotion effect' of this magnetic field on the incidence of lymphoma or leukaemia induced by DMBA (Shen *et al*., 1997).

Groups of female C57BL/6 mice, 28–32 days of age, were either sham-exposed (190 mice) or exposed to ionizing radiation (^{60}Co γ-rays) at 3.0, 4.0 or 5.1 Gy (dose rate, ~ 0.2 Gy/min; 3 groups of 190 mice) or to a 60-Hz magnetic field at a strength of 1.4 mT (380 mice) or to both ionizing radiation and magnetic fields for 18 h per day (3 groups of 380 mice). A group of 380 negative controls was exposed to ambient magnetic field only. All animals were kept until natural death or were killed at 852 days (the mean lifespan of the negative controls). All animals were necropsied and sections of thymus, spleen, lymph nodes, lungs, mainstem bronchi, sternum, kidneys, liver and brain as well as gross lesions in these tissues were examined. Lymphomas were classified as lymphoblastic, lymphocytic, immunoblastic, plasma cell and follicular centre cell. Non-lymphoid tumours included myelogenous leukaemia and histiocytic sarcoma. Because of considerable overlap, the follicular-centre-cell, immunoblastic and plasma-cell lymphomas were combined. There were no significant differences in mortality between the groups. The relative frequencies and general occurrence of haematopoietic neoplasia were similar for both animals exposed to magnetic fields and sham-exposed mice that had received the same ionizing radiation treatment. An exception was the reduced incidence rate of lymphoblastic lymphoma at death in the group exposed to 5.1 Gy and the magnetic field compared to the group exposed to 5.1 Gy only ($p = 0.05$). The total tumour incidences for groups exposed to magnetic fields were not significantly different from those of unexposed animals ($p = 0.55$, χ^2 test). The authors concluded that the

results establish a lack of any overall effect of treatment with a single high level of exposure to magnetic field on the incidence of haematopoietic tumours (Babbitt *et al.*, 2000).

Groups of 50 female CBA/S mice, 3–5 weeks of age, were exposed to ionizing radiation (using a 4- or 6-MV linear accelerator), The total body dose was 4 Gy delivered as three equal fractions of 1.33 Gy at one-week intervals. Simultaneously, the animals were exposed either to a 50-Hz vertical magnetic field of strength 1.26, 12.6 and 126 μT (each applied in succession for 20 min) or were sham-exposed. A third group served as cage controls. The mice were exposed to a magnetic field or sham-exposed for 24 h per day for 1.5 years. In this study, survival until the end of the study in the group exposed to ionizing radiation plus the time-varying magnetic field was 66%, in comparison to a survival until the end of the study of 54% in the group that received ionizing radiation plus sham exposure. The incidence of lymphoma in the group exposed to radiation plus a magnetic field was 22% in comparison to an incidence of lymphoma of 30% in the group treated with radiation plus sham exposure. The authors concluded that the data from this study did not support a role for magnetic fields as a tumour promoter (Heikkinen *et al.*, 2001).

(*b*) *Mouse (genetically modified)*

Groups of 103–111 female (C57BL/LiA × CBA × C57BL/6)fBR-(TG)pim-1 transgenic Eμ-*Pim*-1 (PIM) mice, which carry the *pim*-1 oncogene and are highly sensitive to lymphoma induction by *N*-ethyl-*N*-nitrosourea (ENU), 38–52 days of age, were sham-exposed or exposed to a 50-Hz magnetic field at a field strength of 1, 100, 1000 μT (continuous) or 1000 μT (intermittent 15 min on, 15 min off) for 20 h per day for up to 18 months; a group of 97 female wild-type C57BL/6Ntac mice was sham-exposed. No differences in body weights were observed throughout the experiment. Thirty Eμ-*pim*-1 mice and 30 wild-type mice each received an intraperitoneal injection of 50 mg/kg bw ENU. After nine months of treatment, the incidence of lymphoblastic lymphoma in these controls was 60% in the Eμ-*pim*-1 mice and 5% in the wild-type mice. The incidence of lymphoma (lymphoblastic and non-lymphoblastic) was 2/97 in wild-type mice and 32/111, 31/105, 27/103, 32/105 and 36/104 in the sham-exposed mice and in those exposed to continuous magnetic fields of 1 μT, 100 μT and 1000 μT and those exposed intermittently to 1000 μT, respectively. The incidence of a renal glomerular disease, not associated with lymphoma incidence, varied from 9% to 19% between the groups. All of 12 representative cases of lymphoma expressed the T-cell marker Thy 1, none carried B-cell markers. The authors concluded that, compared to the results of the sham exposure, there was no statistically significant increase in the incidence of lymphoma or its subtypes or in the time to appearance of the tumours in any of the groups exposed to magnetic fields (Harris *et al.*, 1998). [The Working Group noted that the 235 'healthy' survivors from the six groups were not autopsied. This is unlikely to have had an effect on the results obtained using this model since the lymphomas are likely to have been rapidly lethal.]

Groups of 30 male and 30 female Eμ-*pim*-1 mice (see definition above; 'high-incidence' model) [age unspecified] received a single intraperitoneal injection of 25 mg/kg bw ENU followed one day later by exposure to a 60-Hz continuous magnetic field at a field strength of 0 (sham controls), 2, 200 or 1000 μT or to an intermittent field of 1000 μT for 18.5 h per day for 23 weeks. The exposure system has been described by Gauger *et al.* (1999). Groups of 30 male and 30 female TSG-*p53* mice (knock-out; 'low-incidence' model) [age unspecified], not pre-treated with ENU, were either sham-exposed or exposed to a continuous magnetic field of 1000 μT for 18.5 h per day for 23 weeks. All animals underwent a limited gross necropsy. Survival until the end of the study was similar for both strains in all treatment groups, except in Eμ-*pim*-1 males exposed continuously to a magnetic field of 1000 μT (77% versus 60% in sham controls). The incidence of lymphomas in male Eμ-*pim*-1 mice in the sham-exposed group was 59% compared with 47%, 43% and 57% in the groups exposed to fields of 2 or 200 μT, or to the intermittent field of 1000 μT, respectively (not significant). Continuous exposure to the magnetic field at 1000 μT resulted in a decreased lymphoma incidence (23%), which was statistically significant ($p = 0.041$, Fisher's exact test; $p = 0.054$, life-table test). There was no significant difference in the incidence of lymphomas between groups of female Eμ-*pim*-1 mice. The incidence was 49% in sham controls and 45%, 45%, 47% and 53% in the four groups exposed to magnetic fields. In the TSG-*p53* mice, the incidence of lymphoma was 3% in male controls, 0% in exposed males, 3% in female controls and 7% in exposed females (not significant). The authors concluded that their study demonstrated no increased risk of lymphoma in either Eμ-*pim*-1 or TSG-*p53* (knock-out) mice exposed to 60-Hz magnetic fields (McCormick *et al*., 1998).

(*c*) *Other studies*

Although studies with fully transformed cells are outside the immediate scope of this monograph, the Working Group briefly considered a series of in-vivo studies conducted to determine the influence of magnetic fields on the growth and proliferation of transplantable tumour cells. In these studies, mice or rats received injections of leukaemia cells and were subsequently exposed to magnetic fields. The results of these studies were uniformly negative: no effects of exposure to magnetic fields were identified in any study reported (Thomson *et al*., 1988; Sasser *et al*., 1996; Morris *et al*., 1999; Devevey *et al*., 2000).

3.2.5 *Multistage studies of neurogenic cancer*

One study has been conducted to determine the influence of 60-Hz magnetic fields on the induction of neurogenic tumours by transplacental exposure to ENU. On day 18 of gestation, female Fischer 344 rats received a single intravenous dose of ENU (5 mg/kg bw) and were randomized into groups of 32 dams which were either sham-exposed or exposed to magnetic fields at strengths of 2 μT, 20 μT, 200 μT and

2000 μT. The magnetic field exposure system has been described in detail by Mandeville *et al.* (1997). After parturition, dams were exposed to magnetic fields together with their pups until weaning. At weaning, female pups were selected into groups of 50, and exposure to the magnetic fields was continued until study termination at age 65 weeks. A blinded histopathological analysis was performed on the brain (three levels) and spinal cord (three levels) of all animals. Exposure to magnetic fields had no influence on survival in ENU-treated animals. No significant differences between the sham-exposed group and the groups exposed to magnetic fields were seen in the incidence of all neurogenic tumours, glial tumours in the central nervous system or schwannomas in the peripheral nervous system. When compared with a total incidence of neurogenic tumours of 61% (30/49) in sham controls, the incidences of all neurogenic tumours in groups exposed to 60-Hz magnetic fields were 53% (26/49), 56% (28/50), 48% (24/50) and 46% (23/50) in the groups exposed to 2, 20, 200 and 2000 μT, respectively. None of these differences was statistically significant. The authors concluded that their study provided no evidence that 60-Hz magnetic fields have a promoting effect on neurogenic tumours (Mandeville *et al.*, 2000).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Adverse effects other than cancer in humans

4.1.1 *Reproductive and developmental effects*

The effects of two kinds of exposure to magnetic fields are addressed in this section: those associated with power-frequency fields (ELF fields of 50 or 60 Hz) and those associated with video display terminals. The fields associated with video display terminals are typically of varying frequencies in the ELF range as well as higher frequencies (300 Hz–100 kHz). Studies of the possible effects of exposure to such fields on reproductive outcome are discussed below, including some that have examined mutations in maternal or paternal germ cells, investigations of exposure during prenatal development and other possible magnetic field-induced changes in fetal or maternal physiology. The information has been obtained primarily from epidemiological studies and a number of extensive reviews that have been published recently (Chernoff *et al*., 1992; Brent *et al*., 1993; Shaw & Croen, 1993; Huuskonen *et al*., 1998a; Shaw, 2001).

(*a*) *Exposure to ELF electric and magnetic fields during pregnancy*

Studies of maternal exposure to power-frequency fields have focused principally on the use of electric blankets and electrically heated beds, other sources of residential exposure and a few occupational studies.

The use of electric blankets (exclusively older models) and electrically heated beds can add appreciably to total exposure to ELF electric and magnetic fields. It has been estimated that use of electric blankets increases overall exposure to electric fields by 36% over that of non-users (Preston-Martin *et al*., 1988; see also section 1). Although these appliances are frequently used by pregnant women, the available studies present little evidence to support an association of exposure to ELF electric and magnetic fields with adverse reproductive outcomes (Wertheimer & Leeper, 1986; Dlugosz *et al.*, 1992; Juutilainen *et al.*, 1993; Bracken *et al.*, 1995; Li *et al.*, 1995; Belanger *et al.*, 1998). The first suggestion of potential adverse effects came from the study by Wertheimer and Leeper (1986), who reported an increase in the number of spontaneous abortions and of infants who showed below-average fetal growth associated with winter conception, and hence with increased use of electrically heated beds and blankets. However, a number of methodological inadequacies call into question the validity of these results (Hatch, 1992). A subsequent study showed that the use of heated water beds or electric blankets

during pregnancy was not associated with intrauterine growth retardation or reduced birth weight (Bracken *et al*., 1995). The same group also examined the occurrence of spontaneous abortion in pregnant women who used electric blankets or heated water beds: the use of electric blankets did result in an elevated risk ratio (1.8; 95% CI, 1.1–3.1) for spontaneous abortions whereas the use of water beds in homes with wire codes associated with elevated ELF electric and magnetic fields did not increase the risk ratios (Belanger *et al*., 1998).

In a case–control study that examined specific congenital malformations, cleft palate (n = 121), cleft lip (n = 197), anencephalus and spina bifida (n = 224), no effects on odds ratios were evident in the offspring of women who had been exposed to ELF electric and magnetic fields through the use of electric blankets or electrically heated beds (Dlugosz *et al*., 1992). The possible association of neural tube defects with the use of heated beds and blankets by pregnant women was assessed in the offspring of a cohort of 23 491 women (Milunsky *et al*., 1992). No evidence of an association was observed between the use of electric blankets and adverse pregnancy outcomes.

Three studies examining maternal exposure to ELF fields and the risk for cancer in the children exposed *in utero* are reviewed in section 2.2.

In the study of Li *et al*. (1995), the use of electric blankets was not associated with increased anomalies of the urinary tract (odds ratio, 1.1; 95% CI, 0.5–2.3). In a subgroup of women (n = 5) with a history of reduced fertility an odds ratio of 4.4 (95% CI, 0.9–23) was observed.

[The Working Group noted the problem in the interpretation of the data on heated beds arising from the potentially large variability in exposure. This is due both to recall bias on duration and frequency of use and power setting of the appliance and to the large variation in the strengths of the fields produced by the different appliances.]

The studies on the effects of residential exposure (other than from heated beds) on pregnancy outcome have focused primarily on spontaneous abortion and birth weight of the offspring. The first such study (Wertheimer & Leeper, 1989) reported a positive correlation between elevated exposure to ELF magnetic fields at ~ 1 μT in electrically heated homes (from electric heating elements in the ceiling) and fetal loss. In another study, in which ELF magnetic fields were measured in the home, an association was also observed between higher fields (average > 0.2 μT; > 0.6 μT at the front door) and spontaneous abortion in early pregnancy (Juutilainen *et al*., 1993). In contrast, a subsequent study showed no association between exposure to measured magnetic fields above 0.2 μT, or to high wire-codes, and adverse pregnancy outcome, including miscarriage, low birth weight or pre-term delivery (Savitz & Ananth, 1994). Another study that found no relationship between exposure to magnetic fields > 0.2 μT and reduced birth weight or growth retardation was reported by Bracken *et al*. (1995).

Few studies of occupational exposure of women to ELF magnetic fields in relation to pregnancy outcome have been made. In a study of women involved in the manufacturing of semiconductors, no increase in the risk for spontaneous abortion was

observed even for workers exposed to the strongest fields (time-weighted average (TWA) ≥ 0.9 μT) (Swan *et al*., 1995).

A prospective cohort study was conducted to assess the effects of exposure to ELF magnetic fields on spontaneous abortion. Exposure was measured by a dosimeter worn on the body. A weak, non-significant association was observed with exposure to fields above 0.2 μT when the TWA was used as the exposure metric. However, a significantly increased risk (approximately threefold) was found when the exposure metric used was maximum exposure above 1.6 μT. The risk was limited to women who indicated that measurements had been taken during a 'typical' day and was further increased if the subjects had a history of difficulties during pregnancy (Li *et al.*, 2001).

(*b*) *Paternal exposure to ELF electric and magnetic fields*

The investigations of the relationship between paternal exposure to ELF electric and magnetic fields and potentially adverse reproductive outcomes have been almost exclusively conducted in occupational settings. The available studies have largely focused on cancer in the offspring; however, a number of other end-points have also been investigated, including male infertility, perinatal death, spontaneous abortion, congenital anomalies, number of offspring, male:female birth ratio and low birth weight.

The studies examining risk for childhood cancer associated with paternal exposure to ELF electric and magnetic fields are reviewed in section 2.2.

The frequency of abnormal pregnancy outcome (described as congenital malformations and fertility difficulties) was reported to be significantly increased among the wives of workers in high-voltage switchyards (Nordström *et al*., 1983). Buiatti *et al*. (1984) found more cases of male infertility in radioelectrical workers than in controls (odds ratio, 5.9; 95% CI, 0.9–40). No association was seen between semen abnormalities and electrical occupations (Lundsberg *et al*., 1995) and no significant increase in abnormal birth outcome was reported for offspring of power-industry workers (Törnqvist, 1998). Baroncelli *et al*. (1986) reported no effect on the number of children per family when fathers worked in a high-voltage substation. For male workers in industries associated with exposure to ELF fields, the proportion of male offspring was slightly reduced, while the number of offspring of female workers was significantly reduced (Irgens *et al.*, 1997). [The Working Group noted that 'number of children' is a particularly weak end-point with respect to developmental toxicology.]

(*c*) *Exposure to mixed ELF and higher-frequency electric and magnetic fields*

Many of the studies on the relation between exposure to ELF fields and reproductive effects in humans have addressed the question of whether pregnant women are at risk when exposed to the ELF fields associated with video display terminals. Most of these studies have investigated spontaneous abortion and congenital abnormalities in the offspring. There is little evidence for an association between exposure to fields from

video display terminals and spontaneous abortion. Of ten studies (McDonald *et al.*, 1986; Ericson & Källén, 1986a,b; Westerholm & Ericson, 1987; Goldhaber *et al.*, 1988; Bryant & Love, 1989; Windham *et al.*, 1990; Nielsen & Brandt, 1990; Schnorr *et al.*, 1991; Lindbohm *et al.*, 1992), only two showed a significantly increased risk. The study by Goldhaber *et al*. (1988) showed an odds ratio of 1.8 (95% CI, 1.2–2.8), although later analyses suggest that differential reporting of exposure was the source of the association (Hertz-Picciotto *et al*., 1992). Lindbohm *et al*. (1992) observed increased risk ratios among women in Finland who used video display terminals with high-intensity fields (peak-to-peak value, > 0.9 μT) for more than 10 h per week (risk ratio, 3.4; 95% CI, 1.4–8.6). In contrast, a large study conducted in the USA showed no dose–response relationship and no increased risk (Schnorr *et al*., 1991). The strongest fields to which subjects were exposed in this study were weaker than those in the Lindbohm study. Most of the studies reported risk ratios from 1.1 to 1.2 but with 95% confidence intervals that include 1.0. Furthermore, in studies that assessed duration of exposure per day, there was generally no evidence for an increase in risk in association with longer exposure times.

Studies of reproductive health outcomes other than spontaneous abortion have also been made. Low birth weight, pre-term delivery, intrauterine growth retardation and perinatal mortality have been considered when evaluating exposure to fields from video display terminals, but these other end-points have rarely shown any indication of an effect of exposure to ELF fields from video display terminals. Over half a dozen studies (for a review, see Shaw, 2001), including two large studies with more than 1500 cases and 21 000 controls by McDonald *et al*. (1986) and Windham *et al*. (1990), have shown no significant reduction in birth weight associated with use of video display terminals, although intrauterine growth retardation was somewhat elevated (odds ratio, 1.6; 95% CI, 0.92–2.9) with greater use of video display terminals. Elevated risks (odds ratio > 1.5) have occasionally been observed for perinatal death (Bjerkedal & Egenaes, 1987) and congenital abnormalities (Ericson & Källén, 1986a,b); however, the risks were not significantly different from those in controls, and other studies did not confirm the results.

4.1.2 *Immunological effects*

The effects of exposure to magnetic fields on various markers of immune function were studied in two groups of workers: one group comprised 10 hospital personnel operating magnetic resonance tomographs and the other group was composed of 10 industrial workers operating induction heaters. A group of 23 workers served as non-exposed controls. Operaters of magnetic resonance tomographs exposed to static magnetic fields at ≥ 0.5 mT for an indeterminate time showed no significant reductions in their concentration of interleukin-2 or the number of monocytes in their blood. The operaters of induction heaters had been exposed to magnetic fields at either 50–600 Hz (up to 2 mT) or to 2.8–21 kHz (0.13–2 mT) for at least two years, and often longer than five years. The numbers of natural killer cells and monocytes were significantly

increased in the exposed group while monocytes had significantly reduced phagocytic activity compared with those from unexposed personnel. For the two subjects with the highest exposure, the natural killer cell counts were > 700 cells/μL blood compared with 276 ± 124 cells/μL for the controls. Blood samples drawn from these two subjects eight months later still showed elevated counts of natural killer cells (671 and 1202 cells/μL, respectively) while controls had 281 ± 115 cells/μL, indicating that the elevated readings had not been due to an unknown confounding factor at the time of the first blood sampling (Tuschl *et al.*, 2000).

A group of 16 young men aged 20–30 years were exposed to 50-Hz, 10-μT magnetic fields from 23.00 to 08.00. In the first experiment, exposure was continuous for one night, in a second experiment exposure was intermittent, i.e. 1 h 'off' and 1 h during which the field was switched between 'on' and 'off' every 15 s. Sixteen other men were the sham-exposed controls. Blood samples were collected at 3-hourly intervals from 11.00 to 20.00 and hourly from 22.00 to 08.00. No significant differences were observed between exposed and sham-exposed men in haemoglobin concentration, haematocrit, or counts of erythrocytes, platelets, total leukocytes, monocytes, lymphocytes, eosinophils or neutrophils. The numbers of CD3, CD4, CD8, natural killer cells and B cells were also comparable between the two groups (Selmaoui *et al.*, 1996a).

4.1.3 *Haematological effects*

A survey of neurovegetative disorders and haematological effects was conducted in a group of three men and 10 women who had worked near electrical transformers, high-tension cabling (13 kV) and a power generator. In one room the 50-Hz field was 1.2–6.6 μT at floor level and 0.3–1.2 μT at 1.5 m above floor level. The magnetic fields in an adjacent room also used by the group were 0.2–0.3 μT and 0.09–0.12 μT, respectively. The subjects had worked on the premises for at least 8 h per day for one to five years. The occurrence of neurovegetative disorders was assessed from self-rating questionnaires completed by the exposed workers and matched control groups. A comparative analysis of the questionnaires showed that the exposed group suffered a significant increase in physical fatigue, psychological asthenia, lipothymia, decreased libido, melancholy, depressive tendency and irritability. [The Working Group noted the possibility of subjective bias in self-reporting questionnaires.] There was also a significant decrease in total lymphocytes and CD2, CD3 and CD4 lymphocytes, as well as an increase in the number of natural killer cells. Leukopenia and neutropenia were seen in two subjects who were chronically exposed to a field strength of 1.2–6.6 μT. The effects disappeared when exposure stopped, and reappeared when exposure was resumed (Bonhomme-Faivre *et al.*, 1998).

4.1.4 *Neuroendocrine effects*

Melatonin, a hormone produced in the mammalian pineal gland, is secreted in a circadian pattern to give high concentrations at night and low concentrations during the day. The circadian release of melatonin is known to influence certain physiological functions and to modulate the release of other hormones. Although relatively little is known about the mechanism by which changes in melatonin in humans may affect health and well-being, plausible hypotheses exist which suggest that alterations in this hormone may influence the risk for cancer.

On the basis of experimental studies that showed reductions in melatonin concentrations in animals exposed to ELF electric or magnetic fields, Stevens (1987) proposed what has been described as the 'melatonin hypothesis' (Stevens, 1987; Stevens & Davis, 1996). Exposure-related suppression of the night-time rise in melatonin concentration may explain the adverse health outcomes, including cancer — specifically breast or prostate cancer — reproductive problems and neurodegenerative diseases (Wilson *et al.*, 1989). A prerequisite to establishing the relevance and validity of the melatonin hypothesis in humans exposed to ELF electric and magnetic fields would be to determine whether melatonin is indeed suppressed during or following exposure.

(*a*) *Exposure under laboratory conditions*

Studies of endocrine function in humans exposed to 50- or 60-Hz magnetic fields under laboratory conditions have been conducted in four laboratories. As shown in Table 34, the results have been principally negative with respect to the demonstration of exposure-related effects. Night-time exposure of human volunteers to magnetic fields under controlled exposure and lighting conditions had no apparent effect on nocturnal blood concentrations of melatonin when compared with sham-exposed subjects. Endocrine parameters, other than melatonin, have not been shown to be affected by exposure to 50- or 60-Hz electric or magnetic fields.

In the first of a series of double-blind studies, 33 young male volunteers, aged 18–35 years, were exposed to intermittent, circularly polarized magnetic fields of 1 μT or 20 μT, or sham-exposed (11 subjects per group) between 23.00 and 07.00 under controlled environmental and exposure conditions (Graham *et al.*, 1996). Overall, exposure had no effect on melatonin concentrations in serum, as measured by radioimmunoassay. However, men with a pre-existing low melatonin production showed significantly reduced melatonin concentrations when exposed to the 20-μT field. In a second experiment, 40 men were identified who had low melatonin concentrations in their serum. Each of these volunteers slept in the exposure facility for two nights. On one night the men were sham-exposed and on the other they were exposed to 60-Hz, 20-μT magnetic fields. In this experiment, exposure had no effect on melatonin concentrations and the original finding was not replicated in these low-melatonin subjects (Graham *et al.*, 1996). In a third study, using a cross-over design in which each subject served as his own control, 40 young men were sham-exposed for one

Table 34. Melatonin levels in human volunteers

Reference	Assay	Exposure	Response	Comment
Wilson *et al.* (1990)	Early morning excretion of urinary metabolite of melatonin	60-Hz EMFs generated by pulsed alternating or direct current supply to electric blankets at night for 7–10 weeks	No overall effect; transient increases in 7/28 users of one type of blanket	Realistic, but concomitant lack of control over lifestyle
Graham *et al.* (1996)	Night-time serum melatonin concentrations	60-Hz, intermittent fields of 1 or 20 μT for 8 h at night	No effect; possible effect on low-melatonin subjects not replicated in larger study	
Graham *et al.* (1997)	Night-time serum melatonin concentrations	60-Hz, continuous fields of 1 or 20 μT for 8 h at night	No effect	
Selmaoui *et al.* (1996b)	Night-time serum melatonin concentrations and excretion of its major urinary metabolite	50-Hz, continuous or intermittent fields of 10 μT for 9 h at night	No effect	
Wood *et al.* (1998)	Night-time serum melatonin concentrations	50-Hz intermittent sinusoidal or square-wave fields of 20 μT for 1.5–4 h at night	Possible delay and reduction of night-time melatonin concentrations in subgroup	Inconsistent, variable data; incomplete volunteer participation
Graham *et al.* (2000a)	Early morning excretion of urinary melatonin and its metabolite	60-Hz circularly polarized magnetic field of 28.3 μT overnight for 4 consecutive nights	No effect on night-time concentrations	Exposed subjects showed less intra-individual consistency on night 4

From NRPB (2001)
EMF, electric and magnetic field

night and exposed continuously through the second night to a 60-Hz, 20-μT magnetic field. Again, no overall effects on melatonin were found (Graham *et al*., 1997).

Another study conducted in the same laboratory examined 30 healthy young male volunteers who were exposed to 60-Hz, 28.3-μT magnetic fields for four consecutive nights (Graham *et al*., 2000a). Melatonin concentrations were determined by measurement of 6-hydroxymelatonin sulfate (a major melatonin metabolite) in the morning urine samples each day. Again, no overall effect of exposure on melatonin concentrations was observed. The consistency of intra-individual urinary measurements over the four test nights was much higher in the control samples than in those of the exposed subjects.

In a study of the effects of exposure to a 50-Hz, 1-μT magnetic field on sleep patterns in eight women and 10 men, Åkerstedt *et al*. (1999) measured concentrations of melatonin, growth hormone, prolactin, testosterone and cortisol in peripheral blood during a night of sham exposure or a night of exposure to the magnetic field. Exposure to the magnetic field showed effects on sleep patterns, but no significant endocrine or neuroendocrine effects due to exposure were observed.

The other major laboratory study on neuroendocrine effects measured not only melatonin but also pituitary, thyroid and adrenocortical hormones in 32 young men aged 20–30 years who were divided into three groups that were sham-exposed or exposed to continuous or intermittent linearly polarized 10-μT magnetic fields. The exposure-treatments and sampling of serum and urine were conducted over two 24-h periods. No significant differences in serum melatonin and urinary 6-hydroxymelatonin sulfate were found between the test and control groups (Selmaoui *et al*., 1996b). There were also no differences observed in the concentrations or circadian variations of thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, triiodothyronine, thyroxine, thyroxine-binding globulin, cortisol, 17-hydroxycorticosteroids or on thyroxine-binding index (Selmaoui *et al*., 1997).

In another study (Wood *et al*., 1998), the effect of exposure to magnetic fields on melatonin patterns was evaluated in 30 male volunteers. Once the nocturnal melatonin curve had been determined for each individual, the subjects were divided into groups that were either sham-exposed or exposed to magnetic fields (50 Hz, 20 μT) before, during or after the time of peak concentration of melatonin. Exposure preceding the rising segment of the curve significantly delayed the peak in one exposed individual and showed a similar trend in others. The authors noted the suggestive nature of their results but considered them to be preliminary. [The Working Group noted that this is the only laboratory study in humans which sugggested an apparent effect of exposure to magnetic fields on neuroendocrine parameters, including melatonin. Because of the preliminary nature of this study, a number of concerns have been raised over experimental design and statistical analysis.]

(*b*) *Exposure in occupational and residential environments*

A heterogeneous group of epidemiological studies has also evaluated endocrine function in humans exposed to ELF magnetic fields in the relatively uncontrolled

environment of occupational and residential settings. In contrast to the negative results of laboratory studies, all of these studies noted some perturbation in the excretion of 6-hydroxymelatonin sulfate in exposed groups. The perturbations were not, however, consistent across studies and the exposure parameters also differed from one study to the next; they included use of electric blankets, exposure to 16 $^{2}/_{3}$-Hz fields (for railway engineers) as well as exposure to 60 Hz in residential settings and to 50 Hz and 60 Hz in occupational settings.

One of the earliest studies to measure melatonin via the urinary metabolite hydroxymelatonin sulfate (6-OHMS) focused on users of electric blankets. Forty-two volunteers used standard or modified continuous-polymer-wire blankets for eight weeks. The continuous-polymer-wire blankets produced fields that were 50% stronger than those of conventional blankets (0.66 versus 0.44 μT) and they switched on and off twice as often. The subjects in this study served as their own controls. Seven of 28 volunteers using the continuous-polymer-wire blankets were found to have a statistically significant increase in mean night-time urinary excretion of 6-OHMS at the cessation of exposure. This is the only study to report an increase in melatonin or its metabolite in association with higher-than-background exposure to ELF electric or magnetic fields. No changes were seen in the users of conventional electric blankets (Wilson *et al.*, 1990).

A study of Swiss railway workers compared 66 engineers (average exposure of most-exposed workers, 20 μT) with 42 other employees (train attendants and station managers; average exposure of least-exposed workers, 1 μT). Each volunteer served as his own control. Morning and evening urinary concentrations of 6-OHMS were determined during leisure periods and on the day following resumption of work. Evening concentrations of 6-OHMS appeared to be lower by a factor of 0.81 (95% CI, 0.73–0.90) during workdays compared with leisure days in engine drivers, but not in controls. The evening concentrations recovered significantly during leisure periods, which suggests that the effects were reversible. In contrast, morning concentrations of 6-OHMS from engineers and controls did not differ much between workdays and leisure days (Pfluger & Minder, 1996). [The Working Group noted that the interpretation of this study is hampered by the difficulties in accounting for the effects of shift work in some of the subjects and a crude assessment of exposure. It should also be noted that the predominant exposure is to 16 $^{2}/_{3}$-Hz fields, not the 50- or 60-Hz fields considered in most of the other studies.]

The effects of exposure to 60-Hz magnetic fields (and ambient light) were studied in 142 male electric utility workers. Melatonin was measured as 6-OHMS in post-workshift urinary samples over a three-day sampling period. The groups compared were 29 power generation workers (mean exposure, 0.32 μT), 56 linemen and substation operators (mean exposure, 0.23 μT) and 57 utility maintenance and administrative staff (mean exposure, 0.15 μT). In addition to field intensity measured as TWA fields, the temporal stability of the fields was also determined. Exposure intensity, as measured by the geometric mean magnetic field, was not associated with 6-OHMS

excretion. However, evaluation of the temporal stability parameter showed that men in the highest quartile had lower 6-OHMS concentrations on the second and third days of the sampling period when compared with the men in the lowest quartile (Burch *et al*., 1998, 1999).

The same research team studied workers in substations in three-phase environments compared with workers in one-phase environments. Over three consecutive workdays, an apparent field-dependent reduction in mean nocturnal and post-work concentrations of 6-OHMS was reported for men who worked more than 2 h per day in a substation with a three-phase environment. No difference was observed among those men who worked 2 h or less or those who worked in one-phase environments (Burch *et al.*, 2000).

A third occupational study was carried out among female garment-industry workers including 39 production workers and 21 office workers, who served as controls. Exposure assessment varied with the type of machine used and was based on magnetic field measurements made around each type of machine. Exposure to 50-Hz magnetic fields was quite high (> 1 μT) for one group, approximately 0.3–1 μT for a second exposure group and about 0.15 μT for the control group. Morning void urine samples were collected on the Friday and Monday for three consecutive weeks. The average 6-OHMS concentration in the urine on Fridays was lower in the factory workers than in the control group, but no monotonic dose–response pattern was observed. The 6-OHMS concentrations measured in urine samples taken on Monday and Friday were not different for test subjects and controls. Multivariate analysis identified exposure to a magnetic field, smoking and age as significant explanatory variables associated with decreased 6-OHMS excretion (Juutilainen *et al.*, 2000).

The most comprehensive study of the effects of residential exposure to magnetic fields on neuroendocrine response was conducted in Seattle, Washington. The 203 participants were women selected from a group that participated as controls in a case–control study of breast cancer and exposure to electric and magnetic fields. Magnetic fields were measured in the participants' bedrooms, and personal field measurements were made during the same 72 h. Total night-time urine samples collected during the three consecutive nights of the measurement period were used to assess the concentration of 6-OHMS. The results showed that decreasing concentrations of 6-OHMS in the night-time urine were associated with increasing magnetic field strength, as measured in the women's bedrooms at night. The magnetic field effect was seen primarily in women who used medication (e.g. beta blockers, calcium-channel blockers and psychotropic drugs), and was strongest during the times of the year with the shortest nights. These findings were particularly marked when the exposure measure was the proportion of night-time magnetic field measurements ≥ 0.2 μT. The reduction in the concentration of 6-OHMS in urine was not correlated with personal field measurements > 0.2 μT, variability in field measurements, use of electric blankets or wire codes (Davis *et al.*, 2001). [The Working Group noted that

extensive field assessment data were collected and analysed in this study and considerable effort had been made to consider and control potential confounding.]

4.1.5 *Behavioural and physiological effects*

A number of volunteer studies have investigated the effects of static or ELF electric and/or magnetic fields on perception, the electrical activity of the brain, memory and reasoning, mood, hypersensitivity and heart rate.

(*a*) *Static fields*

Prior to the development of magnetic resonance imaging (MRI) techniques, few studies of the effects of static magnetic fields on volunteers had been documented (summarized by WHO, 1987), although various anecdotal reports from laboratories using large accelerators existed. However, with the advent of superconducting magnet technology and MRI in the late 1970s, volunteers could be routinely exposed to static fields ≥ 1.5 T. Most of the reported effects of acute exposure are consistent with known mechanisms of action.

(i) *Perception of electric fields*

The electric charge induced on the surface of a person exposed to a static electric field can be perceived by its interaction with body hair, particularly on the head. Clairmont *et al*. (1989) reported that volunteers had a threshold of perception around 20 kV/m, and that fields above about 25 kV/m produced annoying sensations.

(ii) *Perception of magnetic fields*

Schenck *et al*. (1992) reported dose-dependent sensations of vertigo, nausea and a metallic taste in the mouth in volunteers exposed in MRI systems to static magnetic fields of 1.5 or 4 T; however, gradient and higher-frequency magnetic fields also seem to have contributed to the total exposure. The sensations reported occurred only during movement of the head. In addition, magnetic phosphenes (described below) could sometimes be seen during eye movement in a static magnetic field of at least 2 T.

(iii) *Cognition*

In a static field, Lorentz forces will be exerted on the ion flow through nerve membranes, although these may not be of biological significance at field strengths < 2 T (Tenforde, 1992). The possible cognitive effects immediately after volunteers had been exposed for one hour to a static magnetic field of 8 T were investigated by Kangarlu *et al*. (1999). The written and oral tests comprised a standard ‘mini-mental’ status examination of cognitive function and other standard tests of cognition and motor function. The performance in these tests after exposure did not differ from that in the tests conducted before exposure. An earlier study of a large number of volunteers had reported a lack of effect of exposure to static magnetic fields from magnetic resonance imaging

equipment of 0.15 T in a variety of cognitive tests, although anxiety was increased in the exposed group following exposure (Sweetland *et al*., 1987).

(iv) *Cardiac effects*

On theoretical grounds, Kinouchi *et al*. (1996) noted that the Lorentz force exerted on the blood flow generates an electrical potential across the blood vessel. In practice, so-called 'flow' potentials are readily demonstrated in large animal species, such as dogs, baboons and other monkeys exposed to static fields stronger than ~ 0.1 T. Generally, the largest flow potentials occur across the aorta after ventricular contraction and appear superimposed on the T-wave of the electrocardiogram (Tenforde, 1992).

In addition, a 5–10% reduction in blood flow in the aorta is predicted to occur in static fields of 10–15 T, due to magneto–hydrodynamic interactions (Kinouchi *et al.*, 1996). However, Kangarlu *et al*. (1999) noted that following exposure to an 8-T static field, volunteers showed no change in heart rate or diastolic or systolic blood pressure, compared with values measured before exposure; the values recorded during exposure were also reported as unchanged.

(*b*) *ELF electric and magnetic fields*

The nervous system functions by virtue of electrical signals and may be thought particularly vulnerable to ELF electric and magnetic fields. Various studies have been carried out on the effects of ELF electric and magnetic fields on perception, electrical activity of the brain, cognitive processes (i.e. thinking and memory), mood, hypersensitivity, sleep and heart rate.

(i) *Perception of electric fields*

It is well established that ELF electric fields can be perceived due to the field-induced vibration of body hair. The threshold for perception by hair vibration shows wide individual variation: 10% of exposed subjects were found to have detection thresholds of 10–15 kV/m at 50–60 Hz, and 5% of subjects could detect fields as weak as 3–5 kV/m. Although these effects are not considered to be a hazard, hair vibration and tingling became an annoyance to test subjects at field strengths > 20 kV/m (Deno & Zaffanella, 1975). Of greater biological significance may be the occurrence of capacitive spark discharges or microshocks, generated when two objects of different potential come into close proximity and the electric breakdown field strength of the air is exceeded. The threshold for the perception of spark discharges by a small proportion (10%) of a group of volunteers close to a grounded object has been reported to be 0.6–1.5 kV/m at 50 or 60 Hz, while the threshold was 2.5–6 kV/m for the rest of the group (Bernhardt, 1988).

(ii) *Magnetic phosphenes*

Exposure to power-frequency magnetic fields < 1 mT is generally regarded as imperceptible. In contrast, exposure of the head to magnetic flux densities at 20 Hz above about 5 mT up to about 50 Hz, 15 mT, will reliably induce faint, flickering,

visual sensations called magnetic phosphenes (Lövsund *et al*., 1979, 1980a,b). Similar sensations can be induced by electric currents applied directly via electrodes attached to the head (Lövsund *et al*., 1980b). It is generally agreed that phosphenes result from the interaction of the induced electric current with electrically sensitive cells in the retina. The maximum current density in the retina associated with the generation of magnetically induced phosphenes has been estimated to be about 11 mA/m^2 at 20 Hz (Wake *et al*., 1998), based on calculations using a realistic, electrically heterogeneous model of the human head.

(iii) *Electroencephalograms and event-related brain potentials*

The electrical activity of the brain, recorded as an electroencephalogram, conveys information of a general nature that characterizes the mental state of a person. The electroencephalogram is used in the diagnosis of a variety of pathological conditions. Event-related brain potentials, which are also recorded using electrodes placed on the scalp, convey more specific information concerning brain activity evoked by a sensory stimulus (evoked potentials) and, after about 100 min, by subsequent cognitive processes.

Two double-blind studies on the effects of exposure to 45-Hz, 1000 Amps/m [1.26 mT], magnetic fields on electroencephalograms have been reported. Changes were observed in the alpha, delta and beta frequency bands and in auditory evoked potentials (Lyskov *et al*., 1993a,b). A phase reversal and a slower decrease in the amplitude of the major components of visual evoked potentials have been reported during exposure to very intense (60 mT), pulsed magnetic fields, although they had no effect on visual acuity (Silny, 1984, 1985, 1986). In contrast, no marked effect on visual, auditory or somatosensory evoked potentials was reported during exposure to fields of weaker intensity (28 μT) (Graham *et al*., 1999).

The possible effects of electromagnetic fields on event-related potentials have been investigated mostly in conjunction with various cognitive tests. In general, few effects have been found; those that were noted have tended to be subtle and transitory (Crasson *et al*., 1999). For example, small changes in latency and amplitude of a late component (P300) of the event-related potential associated with cognitive function were observed when subjects exposed to combined electric (9-kV/m) and magnetic (20-μT) fields were asked to discriminate between frequent and infrequent stimuli (Cook *et al*., 1992; Graham *et al*., 1994). When subjects were exposed to a magnetic field of 50 Hz, 100 μT, changes were observed in event-related brain potentials during performance of a listening task, in which auditory discrimination is tested (Crasson *et al*., 1999).

(iv) *Cognition*

A number of studies have looked for evidence of changes in cognitive ability during or after exposure to power-frequency electromagnetic fields. Reaction time, vigilance or sustained attention, memory function, and tasks involving time perception

and information processing have all been tested. Some changes have been reported, but the effects were not consistent between studies. For example, studies have reported both increases (Cook *et al*., 1992; Kazantzis *et al*., 1996) and decreases (Graham *et al*., 1994; Preece *et al*., 1998) in the accuracy of task performance. Similarly, several studies have reported decreased reaction time (Graham *et al*., 1994; Whittington *et al*., 1996), or no effect (Podd *et al*., 1995; Preece *et al*., 1998).

(v) *Mood*

The possibility that environmental exposure to power-frequency electromagnetic fields might be associated with a variety of negative mood states has been assessed in several double-blind laboratory studies in which volunteers have completed mood assessment checklists before and after exposure. None of these studies (Stollery, 1985; Cook *et al*., 1992; Graham *et al*., 1994; Crasson *et al*., 1999) reported any effects although Stollery (1985) reported decreased arousal in one of two participating groups.

(vi) *Hypersensitivity*

It has been reported that some people are sensitive to electric and magnetic fields. The symptoms of sensitivity include sleep disturbance, general fatigue, difficulty in concentrating, dizziness, eye strain, facial skin problems such as eczema and sensations of itching, burning or stinging. Several double-blind laboratory provocation studies have been carried out. Generally, the patients and volunteers who participated in these studies were not reliably able to identify the presence of electric or magnetic fields, and neither subjective symptoms nor biochemical measures were significantly related to the exposure conditions (Andersson *et al*., 1996; Lonne-Rahm *et al*., 2000).

(vii) *Sleep electrophysiology*

Several studies have examined the effect of exposure to electric and magnetic fields on sleep, monitored using electroencephalograms and self-assessment. One study reported a reduction of 'slow-wave' sleep, total sleep time and depth of sleep in subjects exposed to a relatively weak power-frequency magnetic field (50 Hz, 1 μT) (Åkerstedt *et al*,. 1999). In contrast, another study reported that intermittent exposure to 60-Hz, 28-μT magnetic fields was associated with a poor and irregular pattern of sleep (Graham *et al*., 1999).

(viii) *Heart rate*

A statistically significant slowing of heart rate, recorded as the interbeat interval, during exposure to 60-Hz electric and magnetic fields (9 kV/m and 20 μT) has been reported in several studies (Cook *et al*., 1992; Graham *et al*., 1994). However, these effects were not observed at higher or lower field strengths. No effect on heart rate or blood pressure was seen during acute exposure to 50-Hz, 100-μT magnetic fields (Whittington *et al*., 1996).

A more recent study reported an altered heart rate variability during exposure to an intermittent 60-Hz magnetic field at night (Sastre *et al*., 1998). However, in a

pooled analysis of several studies conducted at the same institute, Graham *et al.* (2000b) later reported that this effect was observed only in studies where hourly blood sampling had taken place as part of a different experiment. The authors hypothesized that blood sampling may have altered the arousal of the subjects, allowing interaction with the magnetic field to affect heart-rate variability.

(*c*) *Epidemiological studies*

Several epidemiological studies have been carried out over the past 20–30 years on the incidence of neurodegenerative diseases, suicide and depression, and cardiovascular disease in relation to occupational or residential exposure to ELF electric and magnetic fields (reviewed in Portier & Wolfe, 1998; International Commission on Non-Ionizing Radiation Protection, 1998).

(i) *Neurodegenerative diseases*

Many studies have focused on amyotrophic lateral sclerosis, a progressive degenerative motor neuron disease, and Alzheimer disease, a progressive irreversible degenerative disease of the brain, in groups of people occupationally exposed to ELF electric and magnetic fields.

Several studies on amyotrophic lateral sclerosis have been published (Deapen & Henderson, 1986; Gunnarsson *et al*., 1992; Davanipour *et al*., 1997; Johansen & Olsen, 1998; Savitz *et al*., 1998a,b). The combined results from the two studies of utility workers (Johansen & Olsen, 1998; Savitz *et al*., 1998a,b) show a clear increase in mortality from amyotrophic lateral sclerosis in association with exposure to ELF magnetic fields. This increase is unlikely to be due to chance but may be confounded by exposure to electric shocks.

Five studies have been conducted on Alzheimer disease in relation to exposure to ELF electric and magnetic fields (Sobel *et al*., 1995, 1996; Feychting *et al*., 1998b; Savitz *et al*., 1998a,b). When all studies are considered together, there appears to be an association between the occurrence of the disease and estimated exposure to ELF electric and magnetic fields. However, since this result is mainly confined to studies with weaker designs, support for the hypothesis of a link between Alzheimer disease and exposure to ELF electric and magnetic fields is weak (International Commission on Non-Ionizing Radiation Protection, 1998).

(ii) *Suicide and depression*

A number of studies have examined possible associations between the incidence of suicide and residential or occupational exposure to ELF electric and magnetic fields (Reichmanis *et al*., 1979; Perry *et al*., 1981; Baris & Armstrong, 1990; Baris *et al*., 1996a,b; Johansen & Olsen, 1998; van Wijngaarden *et al*., 2000). Only the most recent study provides some support for the original findings of Reichmanis *et al.* (1979) and Perry *et al.* (1981) suggesting a relation between suicide and exposure to

magnetic fields from overhead power lines (International Commission on Non-Ionizing Radiation Protection, 1998).

The relationship between the prevalence of depressive symptoms and residential or occupational exposure to ELF electric and magnetic fields has been investigated in several studies (Dowson *et al*., 1988; Poole *et al*., 1993; McMahan *et al*., 1994; Savitz *et al*., 1994; Verkasalo *et al*., 1997). Overall, the findings are inconsistent and difficult to interpret (International Commission on Non-Ionizing Radiation Protection, 1998).

(iii) *Cardiovascular disease*

Reduced heart rate variability after exposure to 60-Hz magnetic fields has been reported (Sastre *et al*., 1998). Although inconsistent with the findings of others (Graham *et al*., 1999), the results suggested that such exposure might be associated with an increased incidence of cardiovascular disease and death. Two studies have examined mortality from cardiovascular disease among electric utility workers (Baris *et al*., 1996b; Savitz *et al*., 1999). The overall mortality from cardiovascular and ischaemic disease was generally lower in the study cohorts than in the general population, although the most recent study (Savitz *et al*., 1999) found that longer duration of employment in jobs with elevated exposure to ELF magnetic fields was associated with an increased risk for death from arrhythmia-related conditions and acute myocardial infarction. Nevertheless, the International Commission on Non-Ionizing Radiation Protection (1998) considered the evidence relating cardiovascular effects to elevated exposure to magnetic fields as weak, and the possible association between exposure and altered autonomic control of the heart is speculative.

4.2 Adverse effects other than cancer in experimental systems

4.2.1 *Reproductive and developmental effects*

(*a*) *Static magnetic fields*

(i) *Homogeneous fields*

The results obtained in studies on reproduction and development and exposure to relatively homogeneous static magnetic fields (fields without strong gradients) consistently fail to indicate any strong, easily detectable adverse effects. No effects have been seen on frog embryos exposed to a static magnetic field of 2.5 kG (0.25 T) (Hansson Mild *et al*., 1981); on prenatal development, based on standard teratological and several postnatal evaluations in gestating mice exposed at 1 T (Konermann & Mönig, 1986); on the development of the testis and epididymis in mice after exposure to 0.5–0.7 T *in utero* (Tablado *et al*., 2000); on reproductive performance in mice exposed to 0.49 T (Grzesik *et al*., 1988), or on spermatogenesis in male mice exposed to 0.3 T (Withers *et al*., 1985). When male and female mice were mated in a 3.5-T magnetic field, the number of gestating mice decreased to 21% compared with 68% after matings under sham-exposure conditions (Zimmermann & Hentschel, 1987). The effect was not seen

if mating occurred after removal from the magnetic field, suggesting that only mating behaviour in the strong magnetic field was affected. No adverse effects on fetal development were observed. In contrast, Strand *et al*. (1983) observed a significant enhancement of fertilization when ova or sperm of rainbow trout (*Salmo gairdneri*) were exposed to a 1-T static magnetic field.

Only two studies have reported significant effects of static magnetic fields on embryonal development.

Batches of fertilized eggs from two species of sea urchin (*Lytechinus pictus* and *Strongylocentrotus purpuratus*) were exposed to fields produced by permanent magnets. Static fields delayed the onset of mitosis in both species by a length of time that was dependent on the time interval between exposure and fertilization. Fields of 30 mT, but not 15 mT, caused an eightfold increase in the incidence of exogastrulation in *L. pictus*, whereas neither of these fields produced exogastrulation in *S. purpuratus* (Levin & Ernst, 1997).

Light microscopy and electron microscopy showed changes in chick embryo cerebella when the embryos were exposed to a 20-mT static field either on day 6 of development or during the first 13 days of development (Espinar *et al*., 1997).

(ii) *Static fields with strong gradients*

Two studies have reported effects of static magnetic fields with high spatial gradients on the embryonic development of frogs. The early embryonic growth of *Rana pipiens* was strongly inhibited in a 1-T field with a gradient of 0.84 T/cm (Neurath, 1968). The rate of malformation was increased in *Xenopus laevis* embryos grown in 1-T magnetic fields with gradients from 10–1000 T/m (Ueno *et al*., 1984). The authors of both studies discussed possible mechanisms related to the effects of magnetic forces on iron-containing molecules and oxygen molecules.

(*b*) *Strong static magnetic fields combined with weaker time-varying fields*

Magnetic resonance imaging produces a combination of strong static magnetic fields, radiofrequency fields and time-varying ELF and very low-frequency gradient fields. Few studies have addressed possible developmental effects of the combined fields typical of magnetic resonance imaging.

No effects were seen on embryonal development of frogs when frog spermatozoa, fertilized eggs or embryos were exposed to a combination of a 7.05-kG (0.705-T) static magnetic field and a 30-MHz radiofrequency field (Prasad *et al*., 1982).

Groups of 15 gestating C57BL/6J mice were subjected to magnetic resonance imaging conditions on day 7 of gestation for 36 min, using a 1.5-T static magnetic field combined with a radiofrequency field of 64 MHz (Tyndall & Sulik, 1991). The incidence of eye malformations — towards which this mouse strain is genetically predisposed — was significantly increased in exposed animals compared with a sham-exposed group. A similar exposure to magnetic resonance imaging conditions also

produced statistically significant effects on crown–rump length and craniofacial perimeter, which are less sensitive teratological parameters in these mice (Tyndall, 1993).

Chick embryos were simultaneously exposed to a static magnetic field of 1.5 T for 6 h and to 64-MHz radiofrequency field pulses and switched magnetic field gradients for 4 h. Hatching time and the migration, proliferation and death of motoneurons in the lateral motor column in the chick were unaffected by exposure under conditions of magnetic resonance imaging. Embryo development proceeded normally. There were no obvious adverse effects of exposure to magnetic resonance on differentiation of the major organs, no increase in the incidence of gross abnormalities and no evidence of lesions and malformations (Yip *et al.*, 1994).

(*c*) *ELF electric fields*

Several studies have addressed possible effects of 60-Hz electric fields on reproduction and development in rats (Charles River CD and Sprague-Dawley), using field strengths of 80 kV/m (Seto *et al*., 1984), 100 kV/m (Sikov *et al*., 1984; Rommereim *et al*., 1987), 112–150 kV/m (Rommereim *et al*., 1989) or 10–130 kV/m (Rommereim *et al*., 1990). The studies involved large group sizes and exposure over several generations. Overall, the studies did not reveal any consistent adverse effects. Malformations were increased and fertility was decreased in one study (Rommereim *et al*., 1987). These effects were not confirmed in a companion replicate experiment or in further studies by the same group.

Exposure to 50-Hz electric fields at 50 kV/m did not have any significant effects on the growth and development of eight-week-old male rats exposed for 8 h per day for four weeks. Negative results were also obtained in rabbits exposed for 16 h per day from the last two weeks of gestation to six weeks after parturition (Portet & Cabanes, 1988).

A three-generation study was conducted on Hanford Miniature swine kept in a 60-Hz, 30-kV/m electric field for 20 h per day, seven days per week. Two teratological evaluations were performed on the offspring of the F_0 generation. The incidence of malformations was decreased in the first teratological evaluation after four months of exposure (significant only if analysed by fetus), but was increased in the second evaluation, after 18 months of exposure. An increased number of malformations was also found in one group of offspring of the F_1 generation at 18 months (exposed *in utero* and from birth), but not in another group of F_1 offspring 10 months later. A complete teratological evaluation was performed only for the latter group of offspring. The inconsistency of these results precludes any conclusion that there is a causal relationship between exposure to an electric field and developmental effects (Sikov *et al.*, 1987).

(*d*) *ELF magnetic fields*

(i) *Mammalian teratological studies*

Mouse

In the experiments of Rivas *et al*. (1985), 25–27 gestating Swiss mice per group were exposed to 50-Hz pulsed magnetic fields at 83 μT or 2.3 mT. The number of live births per litter and the mean birth weight were slightly lower in the exposed animals, but the differences from the controls were not statistically significant.

Gestating CBA/Ca mice were exposed from day 0 to day 18 of gestation to 50-Hz or 20-kHz magnetic fields in two independent experiments. In the first experiment, 55 females were exposed to a field of 50 Hz, 13 μT (sinusoidal) or a field of 20 kHz, 15 μT (peak-to-peak). A group of 45 sham-exposed animals served as controls. The second experiment involved 33 females exposed to a 50-Hz, 130-μT field and 34 controls. In addition to standard teratological evaluation, micronuclei were determined in erythrocytes from maternal bone marrow. The numbers of skeletal variations were increased consistently in all exposed groups. The variations were similar in all exposure groups, and suggestive of decreased ossification. The incidence of fetuses with at least three skeletal variations showed a statistically significant increase in all exposed groups compared with corresponding controls. No other significant differences were found in any other maternal or fetal parameters (Huuskonen *et al.*, 1998b).

Gestating CD-1 mice were either exposed from day 0 to day 17 of gestation to a 50-Hz sinusoidal magnetic field at 20 mT or sham-exposed, and the development of the fetuses was evaluated. A total of 90 exposed and 86 sham-exposed control females were analysed. Exposure to magnetic fields was associated with longer and heavier fetuses at term, even when adjusted for litter size, and the fetuses had fewer external abnormalities. The incidence of fetuses with one or more cervical ribs was significantly increased, but the finding was no longer significant when analysed using methods accounting for possible litter effects. The incidences of external and internal abnormalities and resorptions, and of other parameters measured were unaffected (Kowalczuk *et al*., 1994).

In Hebrew University mouse pre-implantation embryos (94 to 303 per group) exposed to 1-Hz, 20-Hz or 50-Hz magnetic fields, a significant increase in the percentage of embryos with arrested development was seen after 72 h of exposure at 20 Hz or 50 Hz. Inhibition of hatching and further development was seen in more than 50% of blastocysts. No exposure-related differences were noted in the rate of development in those embryos that continued to develop (Zusman *et al.*, 1990).

No consistent effects were seen in preimplantation CBA/S mouse embryos exposed to 50-Hz magnetic fields at 13 μT. The vitality of the embryos was not affected by the exposure, and the timing of the development up to the blastocyst stage was similar to that in controls (Huuskonen *et al.*, 2001b).

Rat

Zecca *et al*. (1985) exposed groups of 10 gestating Sprague-Dawley rats to a 50-Hz, 5.8-mT magnetic field for 3 h per day during the period of organogenesis (days 6–15). No malformations were observed, and the numbers of visceral or skeletal variations were not increased. Resorptions and total post-implantation losses were doubled in the exposed group, but these differences were not statistically significant. [The Working Group noted that the small group sizes meant that the study had very little statistical power to show any effects.]

Huuskonen *et al*. (1993) exposed gestating Wistar rats (70–72 per group) to a 50-Hz, 35.6-μT sinusoidal magnetic field or to a 20-kHz, 15-μT (peak-to-peak) saw-tooth magnetic field on days 0–20 of gestation for 24 h per day. The number of fetuses with minor skeletal anomalies was significantly higher in both exposed groups compared with controls. The number of implants and living fetuses per litter showed a statistically significant increase after exposure to the 50-Hz fields. No effects on the incidence of external or visceral malformations or resorptions were found.

The effects of 50-Hz sinusoidal magnetic fields on embryo implantation, maternal serum estradiol, progesterone, testosterone and melatonin concentrations, and on estrogen and progesterone receptor densities in the uterus were studied during pre-implantation and implantation periods in rats (Huuskonen *et al*., 2001a). Groups of 60 gestating Wistar rats were exposed to the magnetic fields at 10 or 100 A/m (13 or 130 μT) or sham-exposed for 24 h per day from day 0 of gestation, and killed at regular intervals between 70 h and 176 h after ovulation. No effects on the total number of implantations were seen, although there were statistically significant differences in the estrogen-receptor and progesterone-receptor densities at some time points.

The incidence of minor skeletal anomalies in fetuses was significantly increased when Wistar rats (12 dams per group) were exposed continuously to a 50-Hz magnetic field with a flux density of 30 mT from day 1 to day 20 of gestation. Increased skeletal ossification was noted, possibly indicating accelerated prenatal development (extra-thoracic ribs, particularly comma-shaped). Compared with controls a significantly lower number of fetuses with reduced ossification of pelvic bones was also observed, indicating that ossification was accelerated by exposure to a magnetic field (Mevissen *et al*., 1994).

No effects were reported in 175 gestating Sprague-Dawley rats exposed throughout gestation for 20 h per day to a 60-Hz magnetic field at 1000 μT, or in a second group of 174 animals exposed to an average field of 0.6 μT (0.33–1.2 μT) as a result of leakage from the system used to expose the first group. The 170 control animals were exposed to an ambient field of 0.1 μT. A decrease in the number of fetuses per litter was found in the group exposed to 1000 μT in the first study, but this decrease was not repeated in a replicate group in that study. Fetal body weight and incidences of external, visceral and skeletal malformations and variations were similar in all groups, and there were no signs of maternal toxicity (Rommereim *et al*., 1996).

Continuous or intermittent exposure to 60-Hz magnetic fields during the period of major organogenesis had no adverse effects on fetal development or maternal toxicity in Sprague-Dawley rats. In this study, 46–55 gestating females per group were either sham-exposed or exposed for 18.5 h per day to linearly polarized, sinusoidal 60-Hz magnetic fields at flux densities of 2, 200 or 1000 μT, or to intermittent fields (1 h on/1 h off) at 1000 μT from gestation day 6 to day 19. Some statistically significant differences between the exposed and sham-exposed animals were seen among the many parameters measured, but no dose–response relationships or any other consistent patterns suggestive of adverse effects were observed. In contrast, a clear response to a positive control (ethylenethiourea) was reported (Ryan *et al*., 1996).

The possible developmental effects of 180-Hz magnetic fields (third harmonic of 60 Hz) alone or in combination with 60-Hz fields were evaluated in groups of 18–20 Sprague-Dawley rats exposed for 18.5 h per day from gestation day 6 to day 19 to a 60-Hz field or a 180-Hz field at 0.2 mT, or to a 60 + 180-Hz field (10% third harmonic; total field, 0.2 mT). Exposure to a magnetic field had no effects on maternal health, litter size, litter weight or fetal development. The incidence of fetal anomalies was comparable in all groups, with the exception of rib variants, which were increased in the exposed groups, with a statistically significant increase in the group exposed to 60 + 180 Hz. The increase in the number of rib anomalies was within the variation observed in historical controls, and the authors concluded that the effect was not biologically significant (Ryan *et al*., 2000).

In an in-vitro study, Hebrew University Sabra strain rat embryos (10.5 days old) were exposed for 48 h to pulsed magnetic fields at frequencies of 20, 50 or 70 Hz. The number of embryos was 32–40 in the treated groups and 60 in the control group. [The field intensities were not reported.] Exposure to the magnetic fields resulted in retarded development, and an increased incidence of malformed embryos was seen after exposure to 50 and 70 Hz. The main malformations observed were absence of telencephalic, optic and otic vesicles and of forelimb buds (Zusman *et al.*, 1990).

(ii) *Mammalian perinatal exposure and behavioural effects*

One of the most sensitive systems for investigating the impact of putative toxic agents employs the perinatal exposure of animals and the assessment of anomalies in the subsequent adult expression of neural and behavioural responses (Lovely, 1988). However, few studies have been conducted on the potential neurobehavioural teratological effects of in-utero exposure to ELF electric and magnetic fields.

Mouse

In a study of postnatal development and behaviour after prenatal exposure, 21 CD1 mice were exposed throughout gestation to a sinusoidal 50-Hz, 20-mT magnetic field. Three possibly field-dependent effects were noted: exposed animals performed the air-righting reflex about two days earlier than controls; exposed males weighed

significantly less than controls at 30 days of age; and exposed animals remained on a Rota-rod for less time as juveniles than sham-exposed control mice (n = 23). No field-dependent effect on the surface-righting reflex or eye opening was reported, in contrast to the findings of Zusman *et al*. (1990) (see above). There was a suggestion that exposed animals took slightly longer to avoid a cliff edge, but this difference was of borderline significance. In the activity wheel, a slightly increased activity of exposed females and a slightly decreased activity of exposed males was noted compared with control mice, but these effects were not considered by the authors to be of any biological significance. The reduction in running time on a Rota-rod, observed in juvenile mice, may represent an impairment of motor coordination during adolescence induced by the magnetic field. No gross impairments of postnatal development or behaviour were seen in the exposed mice (Sienkiewicz *et al*., 1994).

Seven gestating CD1 mice were exposed for the whole gestation period to a vertical, sinusoidal, 50-Hz magnetic field at 5 mT. Eight control animals were sham-exposed. The male offspring were raised without exposure to magnetic fields, and 10 males per group (no more than two from each litter) were tested at 82–84 days of age for deficits in spatial learning and memory in a radial arm maze. No effects on performance were observed (Sienkiewicz *et al*., 1996).

Rat

In early studies, rats were exposed to 60-Hz electric fields during gestation. The offspring were tested using operant-avoidance behavioural methods at 80 days of age. Perinatally exposed rats performed the task more slowly, but were able to avoid shocks during these tests equally as well as control animals (Persinger & Pear, 1972). Two related studies on postnatal development were reported in which rats were exposed *in utero* to 60-Hz electric fields. In rats exposed *in utero* from gestation day 0 until day 8 after parturition, movement, standing and grooming were increased when compared to controls at 14 days of age. There was a significant decrease in the percentage of exposed offspring displaying the righting reflex. A negative geotropism was seen in exposed offspring in a parallel study where exposure began at day 17 of gestation and was terminated 4 days after weaning. All differences were transient and were no longer evident when the animals were tested at 21 days of age (Sikov *et al*., 1984).

After continuous exposure of dams to a pulsed 20-Hz electromagnetic field throughout gestation, the weight of Sprague-Dawley rat offspring at day 1 of age was reduced but it was increased after exposure to a 100-Hz field. The weights of the offspring of dams exposed to a 50-Hz field were decreased only from 21–28 days of age. When combined into one group, exposed animals showed a statistically significant delay, compared to controls, in eye opening. No effect was seen on the surface-righting reflex (Zusman *et al*., 1990). [The field intensities were not reported.]

Increased male accessory sex-organ weights were noted in Sprague-Dawley rats prenatally exposed to a 15-Hz pulsed magnetic field with 0.3-ms pulse duration and a

peak intensity of 0.8 mT. Gestating animals (6 per group) were exposed for two 15-min periods on days 15–20 of gestation, a period critical for the sexual differentiation of the male rat brain. At parturition, no exposure-related effects on number of live fetuses, average weight or anogenital distance were noted. At day 120 postpartum, the male offspring of the exposed dams exhibited diminished territorial scent-marking behaviour and increased accessory sex-organ weights. Concentrations of circulating testosterone, luteinizing hormone and follicle-stimulating hormone were unchanged, as were epididymal sperm counts. The authors concluded that in-utero exposure to magnetic fields had caused incomplete masculinization (McGivern *et al*., 1990).

The developmental increase in the activity of choline acetyltransferase was examined in the brains of fetuses and offspring from Sprague-Dawley rats exposed to a 60-Hz, 500-mG (50-μT), sinusoidal, circularly polarized magnetic field for one month before gestation and during gestation and lactation. Choline acetyltransferase activity in the brain was assessed at four time points during fetal development and at five and 10 days after parturition. Six animals per group were examined at each time point. No differences were observed between the exposed and control rats (Sakamoto *et al*., 1993).

Female Sprague-Dawley rats were exposed to 60-Hz combined electric and magnetic fields for 23 h per day, from day 5 to day 19 post-conception, to study the effects of exposure on somatic growth and cortical development, as well as biochemical and morphological maturation of the neopallium. The animals were exposed to fields of 1 kV/m and 1 mT, 100 kV/m and 0.1 mT, and 100 kV/m and 1 mT. Pups were killed at birth or on postnatal days 5, 12 or 19 for biochemical and morphological studies. No macroscopic or microscopic changes were observed. A small but significant reduction in cortical weight was observed in rats exposed to 1 kV/m and 1 mT, and a small but significant increase of cortical weight after exposure to 100 kV/m and 0.1 mT. The concentrations of DNA, RNA, protein and cerebroside were measured in the neopallium. Slight but significant reductions in RNA and protein concentrations were measured during the first days of exposure to 100 kV/m and 0.1 mT, and a small reduction in RNA concentration in animals exposed to 100 kV/m and 1 mT. The authors concluded that the exposure had either no effect or else caused minimal changes in somatic growth and cerebral development (Yu *et al*., 1993).

The effects of postnatal exposure to combined electric and magnetic fields (in the same combinations as above) on the development of the cerebellum were studied in newborn Sprague-Dawley rats. The pups were exposed for 7–8 h per day from the day of birth and killed after one, two or three weeks. No morphological changes were observed in the exposed group. There was a small but statistically significant decrease in brain weight in the group exposed to 1 kV/m and 1 mT. The concentrations of DNA and RNA in the cerebellum showed some statistically significant differences after exposure to 1 kV/m and 1 mT and 100 kV/m and 0.1 mT, but not at 100 kV/m and 1 mT. In animals exposed to 1 kV/m and 1 mT, DNA and RNA concentrations were

elevated at six and 13 days, but not at 20 days. In animals exposed to 100 kV/m and 0.1 mT, DNA and RNA concentrations were initially (day 8) lower than in the control animals; concentrations in the exposed and control groups were approximately the same at 14 days and were higher in exposed animals than in controls at 22 days. Protein concentrations were lower in the exposed animals than in controls at eight days, but higher at 14 and 22 days (Gona *et al.*, 1993).

Altered behaviour after perinatal exposure to an electric and magnetic field has been reported. Groups of rats were either sham-exposed or exposed for 20 h per day to a combination of a 60-Hz (30-kV/m) electric and 100-μT magnetic field for 22 days *in utero* and during the first eight days *post partum*. As adults, male rats were trained to perform a multiple, random-interval operant task. The responses of the rats that had been exposed *in utero* to the electric and magnetic field gradually became significantly slower than those of the sham-exposed controls. Once the difference in response rate was established, it was found to persist even after experimental extinction of the response followed by reconditioning. The exposed rats did not differ from sham-exposed controls in terms of body mass, physical appearance, grossly observed activity level or incidence of disease (Salzinger *et al.*, 1990).

(iii) *Mammalian multi-generation studies*

Swiss mice were exposed to 50-Hz pulsed (5 ms) magnetic fields at either 2.3 mT or 83 mT from day 0 to day 120 *post partum* for the first generation, and from conception throughout embryological development and up to day 120 *post partum* for the second generation. In the first generation, no changes were observed in body weights or serum glucose, protein, cholesterol or triglyceride concentrations. In the second generation, the body weights and serum glucose concentrations of the exposed mice were significantly lower at 60 and 120 days *post partum* and the triglyceride concentration was decreased at 120 days, compared to sham-exposed control mice (Rivas *et al.*, 1987).

A study aimed at reproductive assessment by continuous breeding investigated reproductive performance in rats over several generations. Groups of Sprague-Dawley rats (40 breeding pairs per group) were sham-exposed or exposed continuously for 18.5 h per day to linearly polarized, sinusoidal 60-Hz magnetic fields at field strengths of 2, 200 or 1000 μT or to an intermittent (1 hour on, 1 hour off) magnetic field of 1000 μT. No exposure-related toxicity was observed in any of the three generations examined. Fetal viability and body weight were similar in all groups, and there were no differences between test and control groups in any measure of reproductive performance (number of litters per breeding pair, percentage of fertile pairs, latency to parturition, litter size or sex ratio). Teratological examinations were not performed (Ryan *et al.*, 1999).

(iv) *Effects of paternal exposure on mammalian reproduction*

Male OF1 mice were exposed from the age of 6 weeks until adulthood to a sinusoidal 50-Hz, 15-μT magnetic field to study possible alterations in testis histology

and its endocrine function. Female mice that were exposed chronically to the same field from the age of 6 weeks were mated at 20 weeks with the exposed males. The offspring were kept under the same experimental conditions. When the offspring reached sexual maturity, the testes of 30 exposed and 30 control males were analysed. A significant increase in testis size and weight was observed. This increase was associated with increased testosterone concentrations in the interstitial tissue, as was shown by histological analysis. Complete spermatogenesis occurred in both control and exposed animals (Picazo *et al*., 1995).

A flow cytometric study was performed to monitor the effects of a 50-Hz sinusoidal magnetic field on mouse spermatogenesis. Groups of five male hybrid (C57BL/Cne × C3H/Cne)F_1 mice, aged 8–10 weeks, were exposed to a field strength of 1.7 mT for 2 or 4 h. Flow cytometry measurements to distinguish various cell types were performed 7, 14, 21, 28, 35 and 42 days after exposure. No effects were observed in animals exposed for 2 h. In groups exposed for 4 h, a statistically significant decrease in the number of elongated spermatids was observed 28 days after the treatment, suggesting a possible cytotoxic and/or cytostatic effect of the exposure on differentiating spermatogonia (De Vita *et al*., 1995).

Six weeks of continuous exposure to circularly polarized 50-Hz magnetic fields at 1, 5 or 50 μT did not change the plasma testosterone concentration in groups of 48 male Wistar-King rats (Kato *et al*., 1994a).

The possible effects of 50-Hz magnetic fields on the fertility of male rats were investigated in Sprague-Dawley rats, aged 20 weeks, exposed to a sinusoidal, 50-Hz magnetic field at 25 μT for 90 days before they were mated with unexposed females. Ten males per group were used (13 in the control group), and each male was mated with two females. The number of conceptions was significantly decreased from 24/26 (92%) in the control group to 10/20 (50%) in the exposed group. The effect persisted in a second mating at 45 days after cessation of exposure (12 conceptions; 60%), but not at 90 days (16 conceptions; 80%). There was also a significant increase in the total number of resorptions, from two in the female controls to six in the females mated with the exposed males. [As only the total number of resorptions was reported, possible litter effects could not be evaluated.] The numbers of implantations and viable fetuses per litter were not significantly affected. The effect of exposure on the fertility of females (10 animals per group) was also evaluated in this study. The 90-day exposure was carried out under the same conditions as used for the males and resulted in a statistically significant decrease in the number of conceptions, from 100% in the controls to 60% in the exposed females. The mean number of implantations per litter decreased from 9.9 to 4.7 and the mean number of viable fetuses per litter from 9.6 to 4.3. These differences were statistically significant. The total number of resorptions was similar in exposed and control females (Al-Akhras *et al.*, 2001).

(v) *Chick and quail embryos exposed to magnetic fields* in vitro

The initial report of Delgado *et al*. (1982) stated that pulsed magnetic fields at frequencies of 10, 100 and 1000 Hz (pulse duration, 5 ms, peak flux density, 0.12, 1.2 or 12 μT) resulted in a large increase in the percentage of abnormalities noted in chick embryos incubated for two days. In later experiments by the same group, the teratogenic effect seemed to depend on the waveform used (Ubeda *et al*., 1983, 1985). In still later experiments, the effect seemed to depend on the orientation of the chick embryo relative to the geomagnetic field (Ubeda *et al*., 1987). The effect of 100-Hz, 0.4-μT or 1-μT pulsed fields on chick embryos was not always reproducible. In the combined data from 13 experiments (40–50 eggs per experiment), 35% of the exposed and 30% of the control embryos were abnormal. However, there was a significant correlation between the variations in the results and extremely small time-dependent changes in the local geomagnetic field. This finding was interpreted by the authors as suggesting that the effect might occur only at some specific values of the geomagnetic field (Leal *et al.*, 1989).

In all the experiments described above, the chick embryos were examined directly after incubation for 48 h in the magnetic field. Ubeda *et al*. (1994) incubated the eggs for an additional nine days after exposure for 48 h, and the embryos were then inspected in a blinded manner. The group sizes of the exposed and sham-exposed embryos ranged from 72 to 92, and an additional 276 embryos were used as background controls. The 100-Hz fields were similar to those used in previous studies, with 1 μT peak amplitude and 5 ms pulse duration, but two different pulse waveforms were used with rise times of 1.2 and 85 μs. The number of developmental anomalies was increased in the exposed groups, indicating that the abnormalities seen in the previous studies are irreversible. The increase was significant ($p = 0.007$) only for the waveform with the shorter rise time.

Two studies failed to reproduce the results of Delgado *et al*. (1982) (Maffeo *et al*., 1984, 1988). A large well-designed international study (‘Henhouse project’) aimed at replicating Delgado’s results (summarized in Berman *et al*., 1990) was carried out in six separate laboratories using identical equipment and standardized experimental procedures. The eggs, however, came from different sources, and the local geomagnetic fields were different. While the results were not uniform, the combined data showed a significant ($p < 0.001$) increase in abnormal embryos in the exposed group. [The Working Group noted that these results may be compromised by the different field strengths used in different laboratories.]

The experiments of Juutilainen *et al*. (1986) showed a higher percentage of abnormalities compared to controls in chick embryos exposed during the first two days of development to a 100-Hz magnetic field with a pulsed waveform similar to that used by Delgado, but also with sinusoidal and rectangular waveforms. In another series of experiments with sinusoidal waveforms, similar effects were found upon exposure to a wide range of frequencies (Juutilainen & Saali, 1986). The effects of 100-Hz sinusoidal fields with a field strength of 1 A/m (1.3 μT) were confirmed in

experiments with a large number of eggs (Juutilainen, 1986). Further experiments showed similar effects from exposure to 50-Hz sinusoidal fields, and the results suggested that the field strength–response curve has a sharp threshold at 1 A/m (1.3 μT) (Juutilainen *et al*., 1987).

Apart from the extensive series of experiments by Juutilainen and colleagues, there have been few other studies on sinusoidal fields. Cox *et al*. (1993) attempted to replicate in part the findings of Juutilainen *et al*. Two hundred White Leghorn chick eggs were exposed to a 50-Hz, 10-μT magnetic field for 52 h and a second group of 200 eggs was incubated in a background field of 0.2 μT. The incubation was continued for 68 h after removal of the eggs from the magnetic field after which the embryos were examined. No difference in malformation rate was observed between the exposed and control embryos. Most of the experimental conditions in the laboratories of Cox and Juutilainen were similar. However, the static (geomagnetic) field was only 17 μT in Cox's laboratory compared with 44–50 μT in Juutilainen's laboratory.

An extensive series of experiments was conducted to study the effects of pulsed and sinusoidal magnetic fields on chick embryo development, involving over 2500 White Leghorn chick embryos. The experiments were performed over five years in five separate studies. In four of these, a pulsed 100-Hz field with a peak amplitude of 1 μT was used (similar to the field used in the Henhouse study). In the last study, the embryos were exposed for 48 h to a 60-Hz, 4-μT sinusoidal magnetic field. The number of abnormalities was always higher in exposed embryos, but in one of the pulsed-field studies, the difference was small and not statistically significant. Overall, the number of abnormalities was approximately doubled in embryos exposed to the pulsed 100-Hz magnetic fields and approximately tripled by exposure to the sinusoidal 60-Hz magnetic fields. Both effects were highly significant. According to the authors, the lack of response in one of their studies could have been due to a change in the genetic composition of the breeding stock before the start of that study. The authors proposed that genetic differences in susceptibility to magnetic fields may explain the inconsistent results between laboratories (Farrell *et al*., 1997).

The effects of 50-Hz and 100-Hz magnetic fields on the development of quail embryos were investigated in eggs produced by 10 females. Data were reported separately for each female. In each experiment, two eggs from each female were used: one exposed and one control. Sham experiments conducted with 240 eggs showed that there was no difference between the exposure and control locations in the incubator. The eggs were exposed to 50-Hz or 100-Hz magnetic fields with rectangular waveform and intensities of 0.2, 1.2, 3.3 and 3.2 μT. The embryos were exposed for 48 h and then inspected in a blind manner. The number of abnormalities was higher in the exposed embryos than in the controls. However, the increase did not reach statistical significance for the embryos exposed to 50 Hz. Comparison of the data for the individual females suggests that there might be genetic differences in sensitivity (Terol & Panchon, 1995).

(vi) *Other non-mammalian embryos*

Ramirez *et al*. (1983) reported reduced egg laying in fruit flies (*Drosophila melanogaster*) and reduced survival during development after exposure to pulsed 100-Hz, 1.8-mT and sinusoidal 50-Hz, 1-mT magnetic fields. No effects were seen in a similar study using 60-Hz, 1-mT fields (Walters & Carstensen, 1987).

Graham *et al*. (2000c) studied the effects of magnetic fields on 'developmental stability', which describes the ability of an organism to maintain a consistent phenotype under given genetic and environmental conditions. *Drosophila melanogaster* were exposed for their entire lives (egg to adult) to 60-Hz magnetic fields at 1.5 or 80 μT. The exposed flies in both groups showed a significant reduction in body weight, compared to controls. The flies exposed to the 80-μT field showed reduced developmental stability measured both by fluctuating asymmetry (asymmetrical wing veins) and frequency of phenodeviants (fused abdominal segments). [The Working Group noted that developmental stability is a new concept, that could potentially be a very useful tool for detecting relatively weak environmental effects.]

Exposure to sinusoidal magnetic fields of 60 Hz, 0.1 mT has been reported to delay the development of Medaka fish embryos (*Oryzias latipes*) (Cameron *et al*., 1985), sea urchin embryos (*Strongylocentrotus purpuratus*) at 60 Hz, 0.1 mT (Zimmerman *et al*., 1990) and zebrafish embryos (*Dario rerio*) at 50 Hz, 1 mT (Skauli *et al*., 2000). No malformations were found in these studies.

(vii) *Interactions with known teratogens*

Cultures of embryonic cells of *Drosophila melanogaster* were used to assess the potential developmental toxicity of exposure to a 60-Hz, 100-μT field for 16–18 h. Exposure to the magnetic field alone was not teratogenic and exposure did not enhance the effects of retinoic acid, hydroxyurea or cadmium, which were all clearly teratogenic in this model. Additional experiments, in which embryos were exposed at 10 or 100 μT for their entire development up to the adult stage, did not produce a significant increase in developmental abnormalities (Nguyen *et al*., 1995).

Exposure to 50-Hz, 10-mT magnetic fields modified the embryotoxic effect of ionizing radiation on chick embryos, but no effects of exposure to magnetic fields alone were observed. In this study, several experiments were performed with X-ray doses of 4 or 5 Gy given on days 3 or 4 of development. The magnetic field was applied either during the first 2–40 h of embryonic development (before X-ray treatment), or during the 12 h immediately after the X-ray treatment. The embryos were examined at day 9 of development. Embryotoxicity was expressed as the sum of embryonic deaths and malformations. Exposure to the magnetic field before the X-ray treatment seemed to protect the embryos from X-ray-induced toxicity, while an enhancement of the embryotoxicity was seen when exposure to the magnetic field followed the X-ray irradiation. Both the protective effect and the enhancing effect were seen consistently in several experiments and were statistically significant (Pafková & Jerábek, 1994). A similar protective effect against subsequent exposure to the chemical teratogens insulin and

tetracyclin was described for 50-Hz, 10-mT magnetic fields. The authors sought to explain the interactions of magnetic fields with X-rays and chemical teratogens on the basis of magnetic-field-induced oxidative stress (Pafková *et al*., 1996).

4.2.2 *Immunological effects*

(*a*) *In-vivo studies*

(i) *Static fields*

The humoral and cell-mediated immune responses were studied in mice (LAF1/J) following exposure to 1.5-T static magnetic fields for six days. The immune response of spleen lymphocytes to sheep erythrocytes was tested by assaying the number of Jerne plaques formed by spleen lymphocytes, and by measuring the concentration of IgM in the serum. The mitogen-stimulated proliferation index of the spleen lymphocytes was also tested using concanavalin A, phytohaemagglutinin and lipopolysaccharide. In no case did lymphocytes from exposed mice respond differently from those from control animals (Tenforde & Shifrine, 1984).

A series of studies investigated the influence of 60-mT magnets implanted over several brain regions on the immune response in male and female Wistar rats. After implantation, the animals were challenged with sheep erythrocytes or bovine serum albumin and tested 14, 24 and 34 days later. Control rats were implanted with iron beads (and sham-operated, when appropriate, to conform to the treatment of exposed animals). The rats were tested for the plaque-forming cell response, local hypersensitivity skin reactions and experimental allergic encephalomyelitis. The authors reported that placing magnets over each of three regions of the brain could have effects on the immune system not seen in controls (Jankovic *et al*., 1991). Furthermore, while surgical induction of lesions in the brain in the nucleus locus ceruleus or pinealectomy caused a reduced immune response, implantation of the magnets reversed these effects (Jankovic *et al*., 1993a,b). Old rats (aged 22 months) that underwent pinealectomy and magnet implantation also showed recovery of immune responses as did the younger animals in the earlier study (Jankovic *et al*., 1994).

(ii) *ELF electric and magnetic fields*

In a study of the effects of electric fields alone, male and female Swiss-Webster mice were exposed for 30 or 60 days (21 h per day) to 60-Hz electric fields of 100 kV/m. No significant differences in serum immunoglobins (IgG and IgM), complement levels or distribution of T or B lymphocytes were found in comparison with sham-exposed control mice. A statistically significant decrease in leukocyte and lymphocyte counts was found after exposure for 60 days but these counts were elevated compared to controls in a subsequent experiment (Morris & Ragan, 1979).

Male C57BL/6 mice were exposed to 60-Hz, 100-μT magnetic fields for 1, 5, 10, 21, 49 and 105 days. For each exposure period, three replicates were evaluated using a battery of 20 immune assays. When these data were analysed using linear statistical

methods, no significant difference in any immune parameter was found (Marino *et al.*, 2000). [Although the authors noted the increased variance in their data for the two longest exposure times, the Working Group considered this analysis too speculative to include in its evaluation.]

The 7,12-dimethylbenz[*a*]anthracene (DMBA) model for breast cancer was used to study immunological effects in rats exposed to horizontal, 50-Hz, 50-μT magnetic fields for 91 days (24 h per day, seven days per week). The geomagnetic field produced a static component of 16 μT parallel to, and 36 μT perpendicular to, the 50-Hz field. After 13 weeks, a marked suppression in T-cell proliferation capacity under concanavalin A challenge was observed. No change in nocturnal concentrations of serum melatonin was seen in exposed animals after 9 or 12 weeks of exposure (Mevissen *et al.*, 1996b).

Female Sprague-Dawley rats were exposed to magnetic fields of 50 Hz, 0.1 mT (24 h per day, seven days per week) for 2, 4, 8 and 13 weeks. Proliferative capacity and production of interleukin-2 were investigated in primary splenic cultures of T and B lymphocytes. Significantly fewer viable splenic lymphocytes were observed at all times in the exposed animals compared with sham-exposed controls. The proliferation rate of B cells, either unstimulated or stimulated with pokeweed mitogen, was comparable in exposed rats and sham-treated animals. In contrast, the proliferation rate of T cells stimulated with concanavalin A from exposed animals showed a statistically significant increase at two weeks, a slight reduction at four weeks, no statistically significant change at eight weeks and a statistically significant reduction at 13 weeks, compared with controls. Non-stimulated T-cell proliferation was unchanged at these treatment times. The addition of melatonin at 1, 10 and 100 nM did not change the T-cell proliferation rate in concanavalin-A-treated cultures from animals exposed to magnetic fields for two and four weeks nor did the addition of melatonin to these cultures change the T-cell proliferation from that observed in cultures treated with concanavalin A alone. The same was true for sham controls except for one experiment with 100 nM melatonin where the response to concanavalin A and melatonin was significantly higher than the reponse to concanavalin A alone. No changes in production of interleukin-2 were observed after any treatment of B lymphocytes. The authors noted that the triphasic alteration in T-cell function during the 13-week treatment period resembled the responses that are seen during prolonged administration of a chronic mild stress, i.e. activation, tolerance and suppression. They concluded that long-term exposure to magnetic fields may lead to impaired immune surveillance in female rats (Mevissen *et al.*, 1998b).

The activation of interleukins by activated T and B lymphocytes was studied in female Sprague-Dawley rats exposed to 50-Hz, 0.1-mT magnetic fields, under conditions described previously by Mevissen *et al*. (1996b). In the first experiment, DMBA-treated rats were exposed for 14 weeks under conditions that suppressed the T cell-stimulated proliferative response, following exposure to magnetic fields for 13 weeks. This experiment failed to show any difference in production of interleukin-1 by mitogen-

activated B cells between exposed and sham-exposed animals. In the second experiment, non-DMBA-treated rats were exposed for 1, 7 and 14 days to 50-Hz, 0.1-mT magnetic fields. No significant changes were observed in the production of interleukin-1 or interleukin-2 by stimulated B or T cells (Haussler *et al.*, 1999).

Natural and adaptive immunity were studied in rats born and raised for six weeks in a 60-Hz magnetic field for 20 h per day. Twenty days after mating, gestating Fisher F344/N rats were exposed to intensities of 2, 20, 200 μT and 2 mT, or kept under control conditions (< 0.02 μT). At weaning, the offspring were separated from their dams and kept under the same field conditions. The following immunological parameters were examined: total T and B cells; CD5+, CD4+ and CD8+ sub-population pattern and natural killer cell activity in splenic lymphocytes; hydrogen peroxide, nitric oxide and tumour necrosis factor production by peritoneal macrophages. In comparison with the control group, there was a significant reduction in the number of CD5+, CD4+ and CD8+ populations, with the greatest reduction occurring at 2 mT. A smaller but nevertheless significant reduction was observed in CD5+ cells at 200 μT. Linear regression analysis showed a dose–response effect with increasing magnetic field intensity. Furthermore, B lymphocyte populations (Ig+ cells) showed a significant reduction ($p < 0.05$) at 20 and 200 μT, but these results did not show a dose-related response. Natural killer cell activity decreased by 50% ($p < 0.05$) at 2 mT. In peritoneal macrophages, no significant changes were observed in the activity of tumour necrosis factor or secretion of nitric oxide, but background and phorbol ester-stimulated production of hydrogen peroxide increased ($p < 0.05$ and $p < 0.001$, respectively) (Tremblay *et al.*, 1996). [The Working Group noted that the significance of these effects was greatly reduced when a comparison was made with sham-exposed animals; only two end-points remained statistically significant.]

Male and female B6C3F_1 mice and female Fischer 344 rats were exposed continuously (18.5 h per day) to 60-Hz, 0.002-, 0.2- and 1-mT magnetic fields; one additional group was exposed to an intermittent (1 h on, 1 h off) 1-mT magnetic field. After exposure periods of 21, 28 or 90 days the parameters examined included spleen and thymus weights and cellularity, antibody-forming cells, delayed-type hypersensitivity, splenic lymphocyte subsets, susceptibility to infection with *Listeria monocytogenes* and natural killer cell activity. No statistically significant differences were found between exposed and sham-exposed mice, except in the activity of natural killer cells and occasional differences in delayed-type hypersensitivity for which there was no clear dose-related pattern. After 28 days of exposure, the activity of natural killer cells in female mice showed a statistically significant increase only at 1 mT, whereas non-significant increases occurred in a dose-dependent manner. Isolated changes in the activity of natural killer cells were seen in three groups of mice exposed for 42 days. A dose-related reduction in activity of natural killer cells was observed in female mice exposed for 90 days, but this was not consistently reproducible (House *et al.*, 1996).

The influence of 60-Hz magnetic fields on the clinical progression of leukaemia was investigated in male Fischer 344 rats. Large granular lymphocytic leukaemia cells from spleens of leukaemic rats were injected intraperitoneally into young rats, which were subsequently exposed to magnetic fields at either 2 μT or 1 mT, for 20 h per day, seven days per week for five, six, seven, eight, nine or 11 weeks. Changes in growth of the spleen and infiltration of large granular lymphocytic leukaemia cells into the spleen and liver were monitored. No significant and consistent differences were observed between groups exposed to a magnetic field and the control group, whereas progression was enhanced in a positive control group exposed to 5 Gy γ-rays (Morris *et al*., 1999).

A model for transplantable acute myeloid leukaemia in rats was applied to examine the influence of 50-Hz, 0.1-mT magnetic fields. Leukaemic cells were injected intravenously into the lateral tail vein of Norway rats, which were subsequently exposed to the magnetic field for 18 h per day (14.00 to 08.00), seven days a week, for up to 27 days. The geomagnetic field was 47 μT, with projection onto the horizontal axis of 8 μT. The investigators measured survival time, body weight, haematological parameters and infiltration of blood, bone marrow, spleen and liver by leukaemic cells. The results showed no significant changes in rats treated with leukaemic cells and exposed to a magnetic field compared with those injected with leukaemic cells, but not exposed to a magnetic field, for any of the parameters involved in leukaemia progression (Devevey *et al*., 2000).

The effects of 7-Hz and 40-Hz square wave magnetic fields on the immunological response were studied in female Lewis rats. Immediately before exposure, the test rats were injected with emulsified spinal column prepared from female Lewis rats. Groups of rats were exposed to magnetic fields of 0.05 μT or 0.5 μT (peak intensity) of either 7 or 40 Hz for 6 minutes every hour for 8 h per day for 15 days. The field patterns were designed to be similar to those that might occur during geomagnetic storms. After exposure, the brains of the rats were examined for infiltration of lymphocytes (mononuclear cells) and mast cells. In rats exposed to 7-Hz, 0.05-μT fields, there were fewer infiltration foci than in any of the other groups. Rats exposed to 40-Hz, 0.5-μT fields had more foci in the right thalamus while those exposed to 7 Hz at the same intensity showed more foci in the left thalamus. The total number mast cells within the thalamus was also increased by the treatments (Cook *et al.*, 2000).

Eight adult male baboons (*Papio cynocephalus*) were exposed for six weeks to 60-Hz vertical electric fields of 6 kV/m and horizontal magnetic fields of 50 μT. Blood samples taken before exposure, at the end of the period of exposure and six weeks after exposure ended were examined by standard immunological methods to determine total leukocyte count and total T cell (CD3+), T helper cell (CD4+), cytotoxic T cell (CD8+), B cell and natural killer cell numbers. A second experiment was conducted in which six of the eight animals used previously were exposed to higher field intensities: 30-kV/m electric fields and 0.1-mT magnetic fields. In the first experiment, exposure-related reductions ($p < 0.05$) in CD3+ and CD4+ counts, interleukin-2 receptor expression and T-cell proliferation in response to pokeweed mitogen were observed. In the second

experiment, there was a similar but reduced response in these parameters compared with the pre-exposure control values. A comparison of the results in the two experiments showed group × period interactions (indication of significance) for total leukocyte count and CD4+ and CD8+ ratios, but the higher exposures did not show greater effects (Murthy *et al.*, 1995).

(*b*) *In-vitro studies*

(i) *Static fields*

Static magnetic fields generated by a 0.5-T magnetic resonance imaging unit were used to study activation markers and interleukin release in mononuclear cells from human peripheral blood. The cells were exposed to the fields for 2 h at 24 °C, then cultured for 24 h at 37 °C with or without PHA stimulation. The cells were assayed for expression of CD25, CD69 and CD71 by immunofluorescence microscopy, and the concentrations of interferon-γ, tumour necrosis factor α and interleukin-4 were measured in the medium using an enzyme-linked immunosorbent assay. Exposure to the magnetic field caused a reduction in CD69 expression, which was enhanced under PHA stimulation compared with controls. An increased release of interferon-γ and interleukin-4 occurred in unstimulated cells, but a reduced release was seen under PHA stimulation compared to controls. The release of tumour necrosis factor α, interleukin-6 and interleukin-10 was unchanged (Salerno *et al.*, 1999).

Apoptosis, intracellular calcium concentrations and lymphocyte and macrophage functions were measured in C57BL/6 mouse macrophages, splenic lymphocytes and thymic cells exposed for 24 h to static magnetic fields ranging from 25 to 150 mT. Cytofluorometric analysis showed a decreased phagocytic uptake of fluorescent latex microspheres, with a concomitant increase in the concentration of intracellular calcium ions in the macrophages. Exposure to the magnetic fields also decreased the concanavalin A-induced mitogenic response in lymphocytes; this was also associated with increases in calcium ion influx. In addition, exposure gave rise to increased apoptosis in thymic cells, as determined by flow cytometry (Flipo *et al.*, 1998).

(ii) *ELF electric and magnetic fields*

Natural killer cell activity in human peripheral blood was examined following in-vitro exposure to 50-Hz magnetic fields. Phytohaemagglutinin or interleukin-2-stimulated lymphocytes or unstimulated control cells were exposed to 50-Hz magnetic fields before or during cytotoxicity tests, and then mixed with different target cancer cell lines (Daudi, Raji, U937, H14, IGROV, SW626, K562, HL60). Exposure to magnetic fields of 0.1, 0.035, 1.8 and 10 mT, with exposure times between 4 h and 7 days, took place in two independent laboratories. The results from both laboratories showed that exposure to 50-Hz magnetic fields with strengths of up to 10 mT did not affect the cytotoxic activity of human natural killer cells (Ramoni *et al.*, 1995).

Peritoneal mast cells from Sprague-Dawley rats were tested for function and histamine release in response to 48/80 (a standard mast cell-stimulating compound).

The cells were exposed to a 60-Hz, 5-mT magnetic field for periods of 30 min to 2 h, either before or during the test. No significant degranulation occurred during exposure to the magnetic field and the cells showed no reduction in sensitivity to the degranulating agent, 48/80 (Price & Strattan, 1998).

The effect of magnetic fields on intracellular free calcium was studied in thymocytes from Sprague-Dawley rats. The cells were exposed to 50-Hz, 0.1-mT horizontal or vertical magnetic fields or to 50-Hz, 0.14-mT circularly polarized fields for 30 min; the effects of consecutive 20-min periods of exposure to vertical and horizontal magnetic fields were also examined. In addition, control or lectin-activated thymocytes, splenocytes and peripheral blood lymphocytes were exposed to a 50-Hz, 5-mT vertical magnetic field for 30 min. No changes in intracellular free calcium concentration were observed in any of these experiments (Nishimura *et al.*, 1999). Intracellular calcium was also monitored in the Jurkat lymphocyte T-cell line. The cells were pre-incubated for 8 min to establish a baseline, and subsequently exposed for 8 min to a 50-Hz, 0.15-mT magnetic field, or sham-exposed in a blinded fashion. No effects on the concentration of intracellular free calcium were found (Wey *et al.*, 2000).

Mononuclear cells from human peripheral blood were exposed to either static or pulsed, 50-Hz, 3-mT magnetic fields and assayed for proliferative responses and production of the cytokines interleukin-2, interferon-γ and tumour necrosis factor α. Pulsed 50-Hz fields with a 120-ns rise time, a 100-μs fall time and a duty cycle of 2/5 were applied for 15 min every 2 h for 6 h, for a total exposure time of 45 min. Proliferative response was measured with and without PHA stimulation, and cytokine concentrations were determined with biological immunoenzymatic assays. There was no effect of the static or pulsed fields on cell proliferation, and the cytokine concentrations, and transcriptional or translational processes in the exposed cells did not differ from those in the controls (Pessina & Aldinucci, 1997).

In a later study, mononuclear cells from human peripheral blood were exposed for 12 h to pulsed magnetic fields of 50-Hz, 3-mT square waves with a rise time of 120 ns, a fall time of 2 ms and a duty cycle of 1/2. In unstimulated cells, a reduction in tumour necrosis factor α was seen immediately after exposure, but no changes were observed in either interleukin-1β or interleukin-2. In contrast, cells stimulated with PHA immediately before exposure to the fields showed progressive increases ($p < 0.05$) in the concentrations of interleukin-1β and tumour necrosis factor α at 24 and 48 h after treatment. The concentration of interleukin-2 was also increased, but only at the end of exposure; proliferation indices were also significantly increased 48 h after treatment (Pessina & Aldinucci, 1998).

Murine cytotoxic T-lymphocytes were used to target B-lymphocytic tumour cells in a standard assay to test chromium release from the B-lymphocytic tumour cells into the medium as an indicator of cell disruption by the murine cytotoxic T-lymphocytes. The latter were exposed through agar bridges to 60-Hz, sinusoidal electric fields for 48 h at intensities of 0.1, 1 and 10 mV/cm in the medium. Following exposure, a 4-h cytotoxicity assay was performed. The results showed a non-significant reduction (7%) in

cytotoxicity after exposure to 0.1 mV/cm, and significant reductions of 19% ($p < 0.0005$) and 25% ($p < 0.005$) after exposure to 1 and 10 mV/cm, respectively (Lyle *et al.*, 1998).

Human leukocytes exposed at 20 °C to 0.2-, 1- or 3-ms pulses from a spark discharge with electric fields of 2.6 kV/cm and higher — as single pulses and with up to 10 pulses at 5-s intervals — showed that breakdown of the membrane barrier was field intensity-dependent (Hansson Mild *et al*., 1982).

Mononuclear cells obtained from the peripheral blood of 25 healthy donors were exposed for 12 h to a 3-Hz pulsed magnetic field of 4.5 mT, with a 1/2 duty cycle and rise and fall times less than 100 μs (the field was somewhat smoothed due to coil inductance). Each pulse had a maximum value of 13 T/s, which produced a maximum induced electric field in the medium of 23 mV/m. Cell proliferation, as measured by the uptake of tritiated thymidine, was inhibited in mononuclear cells from 24/25 donors, by up to 60%. There were no differences in blastogenic response between exposed and control cultures (Mooney *et al.*, 1986).

4.2.3 *Haematological effects*

(*a*) *Static fields*

Female NMRI mice were exposed to a static magnetic field of 3.5 T. The haematological parameters were generally unaffected. Necropsy and histopathological investigations revealed no pathological alterations (Zimmermann & Hentschel, 1987).

The potential adverse effects of subchronic exposure to a strong static magnetic field were evaluated in adult Fischer rats and their offspring. A battery of clinical tests in adult male and female rats and their offspring detected no adverse biological effects that could be attributed to a 10-week period of exposure to a 9.4-T static magnetic field (High *et al.*, 2000).

(*b*) *ELF electric and magnetic fields*

The acute effects of power-frequency magnetic fields on haematopoiesis were studied in 10-week-old CBA/H mice known to be susceptible to the induction of acute myeloid leukaemia after exposure to ionizing radiation. Mice were exposed to 50-Hz, 20-mT magnetic fields for seven days. Samples of blood and bone marrow were taken from three mice in each group immediately after exposure (day 0) and at about the same time on days 2, 4, 7, 10 and 18. Up to 19 days after exposure, no significant effects on peripheral blood characteristics were observed. Assays of bone-marrow stem cells and myelomonocytic progenitor cells also failed to show significant differences between exposed and control mice (Lorimore *et al.*, 1990).

Spleen colony formation was examined in male CBA mice exposed to 50-Hz, 0.022-mT magnetic fields for 1 h, at the same time of day, for five successive days (5 h per five days). The number of colony-forming units was higher in the exposed animals than in the untreated controls but was not higher than that counted in sham-

exposed animals. Significant changes were seen in the thymus weight and thymus index of exposed animals when compared with both control and sham-exposed animals. In a second study, mice were given a sublethal dose of X-rays (6 Gy) followed 2 h later with the same magnetic field treatment as above, i.e. 5 h every five days. The number of colonies per spleen showed a consistent, significant increase with exposure to the magnetic field and the number of colony forming units per femur was decreased. In a third study, bone marrow was taken from mice that had been exposed to 50-Hz, 0.022-mT magnetic fields for 5 h per five days, and injected into mice that had been exposed to a lethal dose of X-rays (9 Gy). The number of colony forming units per femur in the recipient mice was significantly reduced at days 1 and 4 after injection (Korneva *et al.*, 1999).

Two hundred and forty adult male Sprague-Dawley rats were exposed for 8 h per day to 50-Hz, 25-kV/m or 100-kV/m vertical electric fields for 35, 55 and 155 days and the animals were killed after 140, 164 and 315 days, respectively. Irrespective of the duration of exposure, the mode of grounding and the field strength, no statistical differences in body weight, morphology or histology of the liver, heart, mesenteric lymph nodes or blood parameters were found in the exposed animals compared to controls (Margonato *et al.*, 1993).

Adult male Sprague-Dawley rats were exposed to a 50-Hz magnetic field with a flux density of 5 μT for 22 h per day for 32 weeks. Haematological variables were measured in blood samples taken before exposure to the field and at 12-week intervals during exposure. No differences were detected between the exposed and control groups in haematology and haematochemistry, or in the concentrations of the neurotransmitters dopamine and serotonin in the brain (Margonato *et al.*, 1995).

Adult male Sprague-Dawley rats were exposed for 8 h per day on five days per week for eight months to 50-Hz electric and magnetic fields of two different field strength combinations: 5 μT and 1 kV/m and 100 μT and 5 kV/m. The animals were kept under constant controlled illumination for 24 h per day. Blood samples were collected for determination of haematological variables before exposure and at 12-week intervals during exposure. No pathological changes were observed at either field strength combination in animal growth rate, in morphology and histology of the tissue specimens collected from the liver, heart, mesenteric lymph nodes, testes and bone marrow, or in serum chemistry (Zecca *et al.*, 1998).

Haematological and serum chemistry variables were examined in groups of female Sprague-Dawley rats exposed to uniform, vertical 60-Hz electric fields at 100 kV/m for 15, 30, 60 or 120 days. Another group of rats was sham-exposed. Blood samples were collected from all animals within 3 h after exposure and analysed for leukocyte and erythrocyte counts, haemoglobin concentration, reticulocyte and thrombocyte counts, bone marrow cellularity and prothrombin times, serum iron and serum alkaline phosphatase concentrations and serum triglyceride values. Significant differences between exposed and sham-exposed rats were seldom seen. Statistical evaluation of these data did not detect any consistent effect of the electric field (Ragan *et al.*, 1983).

Groups of Fischer 344/N rats and B6C3F_1 mice were exposed to 60-Hz magnetic fields or sham-exposed for eight weeks. Magnetic field strengths were 0.002, 0.2 and 1 mT. The whole-body exposure was continuous for 18.5 h per day, seven days per week. An additional group of rats and mice was exposed intermittently (1 h on/1 h off) to 1-mT magnetic fields for the same period of time. The animals were kept on a 12 h/12 h light/dark cycle. There were no gross, histological, haematological or biochemical lesions that could be attributed to magnetic field exposure (Boorman *et al.*, 1997).

4.2.4 *Neuroendocrine effects*

The hypothesis that reduced pineal function may promote the development of breast cancer in humans was initially suggested by Cohen *et al.* (1978). Several mechanisms whereby changes in pineal or serum melatonin concentrations may affect the risk for breast cancer have been proposed. These include the observation, at least in some animal species, that decreased melatonin concentrations cause elevations in circulating levels of estrogen and progesterone which increase cell proliferation in the stem cell population of the breast and may thus increase the risk for cancer in this tissue (Cohen *et al.*, 1978). Other authors have suggested that melatonin may directly suppress the growth of human mammary tumour cells (Blask & Hill, 1986) and of cells of other cancer types, particularly melanoma, prostate cancer, ovarian cancer, bladder cancer and leukaemia (Stevens, 1993) and that melatonin may act as a scavenger of free radicals, preventing oxidative damage to DNA (Reiter *et al.*, 1995), at least at pharmacological levels (Cridland *et al.*, 1996). It has also been suggested that melatonin may modulate immune responsiveness (Maestroni *et al.*, 1986).

Studies of the effects of electric and magnetic fields on melatonin concentrations have mostly been carried out in rats but have also used mice, Djungarian hamsters (*Phodopus sungorus*), sheep and primates, including humans. The experimental details of the animal studies are given in Table 35. Human data are discussed in section 4.1.4 and summarized in Table 34.

(*a*) *Electric fields*

Several studies by one group of authors (Wilson *et al.*, 1981, 1986*;* Reiter *et al.* 1988), reported that exposure to electric fields significantly suppressed pineal melatonin and the activity in the pineal gland of the enzyme *N*-acetyltransferase, which is important in the synthesis of melatonin. These effects appeared within three weeks of exposure, but disappeared within three days after cessation of exposure. A similar suppression of pineal melatonin was reported by these authors to occur after the prenatal and neonatal exposure of rats to power-frequency electric fields; no simple dose–response relationship was apparent. Grota *et al*. (1994) reported that exposure of rats to power-frequency electric fields had no effect on pineal melatonin concentrations

Table 35. Studies in animals of melatonin concentrations in response to exposure to ELF electric and magnetic fields

Reference	Assay	Exposure	Response	Comment
ELF electric fields				
Rats				
Wilson *et al.* (1981, 1983)	Night-time pineal melatonin concentrations and NAT enzyme activity in adult rats	60 Hz, 1.7–1.9 kV/m (not 65 kV/m) due to equipment failure; 20 h per day for 30 days	Reduced pineal melatonin and SNAT activity	Data combined in one experiment because of variability
Wilson *et al.* (1986)	Night-time pineal melatonin concentrations and SNAT enzyme activity in adult rats	60 Hz, 65 kV/m (39 kV/m 'effective') for up to 4 weeks	Pineal melatonin and SNAT activity reduced after 3 weeks of exposure; recovered 3 days after exposure ceased	
Reiter *et al.* (1988)	Night-time pineal melatonin concentrations in immature rats	60 Hz, 10, 65 or 130 kV/m during gestation and 23 days postnatally	Night-time peak reduced and delayed in exposed animals	No simple dose–response relationship
Grota *et al.* (1994)	Night-time pineal melatonin concentrations and NAT enzyme activity and serum melatonin in adult rats	60 Hz, 65 kV/m for 20 h per day for 30 days	No effect on night-time melatonin and NAT; serum melatonin decreased	
ELF magnetic fields				
Mice				
Picazo *et al.* (1998)	Serum melatonin concentrations in fourth generation of male mice	50 Hz, 15 μT for four generations	Reduced night-time concentrations	Experimental procedures not fully described
de Bruyn *et al.* (2001)	Night-time plasma melatonin concentrations in mice	50 Hz, 0.5–77 μT (2.75 μT average) 24 h/day from conception to adulthood	No effect	

Table 35 (contd)

Reference	Assay	Exposure	Response	Comment
Rats				
Martinez-Soriano *et al*. (1992)	Serum melatonin concentrations in adult rats	50 Hz, 5 mT for 30 min during the morning for 1, 3, 7, 15 and 21 days	Serum melatonin reduced on day 15 [no values for days 1, 7 or 21]	Technical difficulties; brief description of method
Kato *et al*. (1993)	Pineal and serum melatonin concentrations in adult rats	50 Hz circularly polarized, 1, 5, 50 or 250 μT for 6 weeks	Night-time and some daytime reductions in serum and pineal melatonin	Questionable comparisons with historical controls
Kato *et al*. (1994b)	Serum melatonin concentrations in adult rats	50 Hz, circularly polarized, 1 μT for 6 weeks	Night-time melatonin concentrations reduced, returning to normal within one week	Comparison with sham-exposure
Kato *et al*. (1994c)	Pineal and serum melatonin concentrations in adult, pigmented rats	50 Hz, circularly polarized, 1 μT for 6 weeks	Night-time pineal and serum melatonin concentrations reduced	Comparison with sham-exposed and historical controls
Kato *et al*. (1994d)	Serum melatonin concentrations in adult rats	50 Hz, horizontally or vertically polarized, 1 μT for 6 weeks	No effect	Comparison with sham-exposed and historical controls
Kato *et al*. (1994a)	'Antigonadotrophic' effect of melatonin on serum testosterone in adult rats	50 Hz, circularly polarized, 1, 5 or 50 μT for 6 weeks	No effect	Comparison with sham-exposure
Selmaoui & Touitou (1995)	Night-time serum melatonin concentrations and pineal NAT activity in adult rats	50 Hz, 1, 10 or 100 μT for 12 h once or for 18 h per day for 30 days	Reduced melatonin and NAT activity after 100 μT (acute) and 10 and 100 μT (chronic)	
Bakos *et al*. (1995, 1997, 1999)	Night-time excretion of melatonin urinary metabolite in adult rats	50 Hz, 1, 5, 100 or 500 μT for 24 h	No significant effects compared with baseline pre-exposure controls	

Table 35 (contd)

Reference	Assay	Exposure	Response	Comment
Mevissen *et al.* (1996b)	Night-time pineal melatonin concentrations in non-DMBA-treated adult rats	50 Hz, 10 µT for 13 weeks	No effect	A small part of a larger, well-planned mammary tumour study
Löscher *et al.* (1998)	Night-time serum melatonin concentrations in adult rats	50 Hz, 100 µT for 1 day or 1, 2, 4, 8 or 13 weeks	No consistent efects on melatonin	The few positive effects could not be replicated
John *et al.* (1998)	Night-time excretion of melatonin urinary metabolite in adult rats	60 Hz, 1 mT for 20 h/day for 10 days or 6 weeks; 1 mT intermittent for 1 h or for 20 h/day for 2 days	No effect	
Djungarian hamsters				
Wilson *et al.* (1999)	Night-time pineal melatonin concentrations	60 Hz, 100 µT for 15 min, 2 h before dark	Suppression of night-time peak	
Yellon (1994)	Night-time pineal and serum melatonin concentrations	60 Hz, 100 µT for 15 min, 2 h before dark	Reduced and delayed night-time peak; less effect and absent in 2nd and 3rd replicates, respectively	Considerable variation between replicate studies
Yellon (1996a)	Night-time pineal and serum melatonin concentrations	60 Hz, 100 µT for 15 min, 2 h before dark	Reduced and delayed night-time peak; less effect in second replicate	Considerable variation between replicate studies
Yellon (1996b)	Night-time pineal and serum melatonin concentrations; adult male reproductive status	60 Hz, 100 µT for 15 min, 2 h before dark for 3 weeks	No effect on pineal or serum melatonin; no effect on melatonin-induced sexual atrophy	Second part of above study

Table 35 (contd)

Reference	Assay	Exposure	Response	Comment
Truong *et al*. (1996)	Night-time pineal and serum melatonin concentrations; male puberty, assessed by testes weight	60 Hz, 100 μT for 15 min, 2 h before dark from 16 to 25 days of age	Reduced and delayed night-time peak; this effect absent in second replicate; no effect on development of male puberty	Considerable variability in melatonin concentrations between replicate studies
Truong & Yellon (1997)	Night-time pineal and serum melatonin concentrations	60 Hz, 10 or 100 μT (continuous) or 100 μT (intermittent) for 15 or 60 min before or after onset of dark period	No effect	
Yellon & Truong (1998)	Night-time rise in pineal and serum melatonin concentrations; testes weight	60 Hz, 100 μT in complete darkness; 15 min/day for up to 21 days	No effect, even in the absence of photoperiodic cue	
Niehaus *et al*. (1997)	Night-time pineal and serum melatonin concentrations; testis cell numbers	50 Hz, 450 μT (peak) sinusoidal or 360 μT (peak) rectangular fields, 56 days	Increased cell number and night-time serum melatonin concentrations after exposure to rectangular field	Animals on 'long-day' schedule; difficult to interpret
Wilson *et al.* (1999)	Night-time pineal melatonin concentrations and testis and seminal vesicle weights in short-day (regressed) animals	60 Hz, 100 or 500 μT; continuous and/or intermittent, starting 30 min or 2 h before onset of darkness; for up to 3 h on up to 42 days	Reduced pineal melatonin after acute (15 min) exposure; reduced gonad weight but not melatonin after 42-day exposure	Authors suggest a stress-like effect

Table 35 (contd)

Reference	Assay	Exposure	Response	Comment
ELF electric and magnetic fields				
Suffolk sheep				
Lee *et al*. (1993, 1995)	Night-time serum melatonin concentrations and female puberty, detected by rise in serum progesterone	60-Hz, 6-kV/m and 4-μT fields generated by overhead power lines; 10 months	No effect of electric and magnetic fields; strong seasonal effects	Two replicate studies; open-air conditions
Non-human primates				
Rogers *et al*. (1995a)	Night-time serum melatonin concentration in baboons	60-Hz, 6-kV/m and 50-μT fields (6 weeks), 30-kV/m and 100-μT fields (3 weeks)	No effect	
Rogers *et al*. (1995b)	Night-time serum melatonin concentration in baboons	60-Hz, irregular and intermittent sequence of 6-kV/m and 50-μT fields or 30-kV/m and 100-μT fields accompanied by 'transients'	Reduced serum melatonin levels	Preliminary study on two animals

Data from National Radiological Protection Board (1992, 2001)
DMBA, 7,12-dimethylbenz[*a*]anthracene; NAT, *N*-acetyltransferase; SNAT, serotonin-*N*-acetyltransferase

or activity of *N*-acetyltransferase, although concentrations of serum melatonin were significantly depressed.

The difficulties in reproducing some of the earlier findings on the effects of power-frequency electric fields on melatonin have been discussed by Brady and Reiter (1992).

(*b*) *Magnetic fields*

(i) *Studies in mice*

One large-scale study (National Toxicology Program, 1996) reported that exposure to continuous or intermittent 60-Hz magnetic fields (up to 18.5 mT) had no effect on serum or pineal melatonin concentrations in mice. Chronic exposure to 50-Hz magnetic fields of varying intensity (1–130 μT), as part of a tumour promotion study, was reported to have no effect on the night-time excretion of a urinary metabolite of melatonin in mice that had been pre-exposed to ionizing radiation (4 Gy) (Heikkinen *et al.*, 1999).

(ii) *Studies in rats*

An extensive series of studies was conducted in male rats to assess the effects of exposure to circularly or linearly polarized power-frequency magnetic fields of up to 250 μT for up to six weeks on pineal and serum melatonin concentrations. [The Working Group noted that a major difficulty with the interpretation of the results of many studies by this group was that the sham-exposed rats were sometimes treated as 'low-dose' groups because they were exposed to stray magnetic fields (< 2%) generated by the exposure system; thus, statistical comparison was sometimes made with historical controls. Such procedures fail to allow for the interexperimental variability (Kato *et al.*, 1993, 1994b,c,d).]

In the first study, night-time pineal and serum melatonin concentrations were shown to be significantly reduced after exposure for 6 weeks to circularly polarized power-frequency magnetic fields of up to 250 μT, compared with melatonin concentrations in historical controls; in contrast, there was no difference between the concentrations measured in the exposed and concurrent, sham-exposed groups (Kato *et al.*, 1993). The effect had disappeared one week after cessation of exposure (Kato *et al.*, 1994b). A further study with a different, pigmented, rat strain showed a night-time suppression of serum and pineal melatonin in exposed animals compared with both sham-exposed animals and historical controls (Kato *et al.*, 1994c). In contrast to these results, exposure to horizontally or vertically polarized power-frequency magnetic fields for six weeks had no effect on pineal or serum melatonin when compared to sham-exposed animals and historical controls. The reason for this difference between the effects of circularly polarized and horizontally or vertically polarized fields was not clear (Kato *et al.*, 1994d). The last study of this series tested the hypothesis that a reduction in serum melatonin might be correlated with an increase in serum testosterone. However, animals exposed to circularly polarized 50-Hz magnetic fields

were found to have serum testosterone levels similar to those in their sham-exposed counterparts (Kato *et al.*, 1994a).

Four other groups investigated the effects of magnetic fields on serum and pineal melatonin concentrations in rats and came to inconsistent, but generally negative, conclusions. One study reported that acute or chronic exposure of rats to horizontally polarized power-frequency magnetic fields significantly depressed night-time serum melatonin concentrations and activity of *N*-acetyltransferase in the pineal gland (Selmaoui & Touitou, 1995). In another study, exposure to a vertical or horizontal power-frequency magnetic field (50 Hz, 100 μT) had no effect on the circadian excretion of 6-sulphatoxymelatonin, the major urinary metabolite of melatonin (Bakos *et al.*, 1995, 1997). As part of a larger study on the effects of electromagnetic fields on mammary tumours induced by 7,12-dimethylbenz[*a*]anthracene and pineal function in rats, no effect of exposure to a magnetic field of 50 Hz, 10 μT, continuously for 13 weeks, was found on pineal melatonin concentrations in animals treated with 7,12-dimethylbenz[*a*]anthracene (Mevissen *et al.*, 1996b; see also Löscher *et al.*, 1998). Exposure of rats to power-frequency magnetic fields (60 Hz, 1 mT) for up to six weeks under a variety of conditions intended to maximize magnetic field sensitivity had no effect on the circadian excretion of the major urinary metabolite of melatonin (John *et al.*, 1998).

(iii) *Studies in seasonal breeders*

Four laboratories have investigated the effects of exposure to ELF electric and magnetic fields on pineal activity, serum melatonin concentrations and reproductive development in animals that breed seasonally. Three research groups examined these effects in Djungarian hamsters in which the duration of the night-time rise in melatonin secretion during the shortening days of autumn and winter inhibits reproductive activity.

The most complete data come from a series of studies by Yellon and colleagues. Acute exposure to a power-frequency magnetic field (60 Hz) two hours before the onset of darkness reduced and delayed the night-time rise in serum and pineal melatonin concentration, but this effect was diminished in a second replicate study and absent in the third (Yellon, 1994). Similarly variable results on pineal and serum melatonin concentrations were reported by Yellon (1996a,b) and Truong *et al.* (1996). In addition, both studies found that exposure to a magnetic field had no effect on reproductive development, even in reproductively repressed hamsters kept on ‘short-day’ (winter) light/dark schedules, which might be thought to be sensitive to reduced and delayed night-time melatonin elevation. A fourth study, under experimental conditions that were different from those in the previous studies found no effect of exposure to magnetic fields on the night-time melatonin concentrations (Truong & Yellon, 1997). Finally, a brief exposure to power-frequency magnetic fields before the night-time rise in pineal and serum melatonin concentrations had no effect even in complete darkness, i.e. in the absence of a strong photoperiodic cue (Yellon & Truong, 1998).

In studies from a different laboratory, chronic exposure of Djungarian hamsters, which were kept on 'long-day' (summer) light/dark schedules, to 'rectangular' power-frequency magnetic fields (50 Hz; 360 or 450 μT) was reported to increase testis cell numbers and night-time concentrations of melatonin in serum, whereas exposure to sinusoidal power-frequency magnetic fields had little effect. The authors concluded that the in-vivo effects of magnetic fields may have been dependent on their waveform, and that the rapidly changing waveform of the rectangular fields was a more effective biological stimulus (Niehaus *et al.*, 1997). [The Working Group noted that the results are not easy to interpret: increased melatonin concentrations in the Djungarian hamster are usually accompanied by decreased testicular activity.]

More recently, the effect of exposure to power-frequency (60 Hz) magnetic fields on pineal melatonin concentration, serum prolactin concentration and testicular and seminal vesicle weights have also been studied in Djungarian hamsters that had been shifted to a short-day light/dark regime in order to induce sexual regression. Night-time pineal melatonin concentrations were reduced after acute exposure, but this effect diminished with prolonged exposure. In contrast, induced sexual regression, as indicated by the reduction in testicular and seminal vesicle weights, seemed to be enhanced rather than diminished by prolonged exposure to the magnetic field, suggesting a possible stress response (Wilson *et al.*, 1999).

The fourth set of studies of the effects of electric and magnetic fields on seasonal breeders was conducted with Suffolk sheep, which have a long gestational period and become reproductively active in the autumn, as the day-length shortens. In two replicate studies, Suffolk lambs were exposed outdoors to the magnetic fields generated by overhead transmission lines for about ten months. No effect of exposure was observed on serum melatonin concentrations or on the onset of puberty (Lee *et al.*, 1993, 1995).

(iv) *Studies in non-human primates*

Chronic exposure of three male baboons (*Papio cynocephalus*) to a combination of 60-Hz electric and magnetic fields (6 kV/m, 50 μT and 30 kV/m, 100 μT) for 6 weeks had no effect on night-time serum melatonin concentrations (Rogers *et al.*, 1995a). A preliminary study, based on data from two baboons, showed a marked suppression of the night-time rise in melatonin after exposure of the animals for three weeks to an irregular, intermittent sequence of combined electric and magnetic fields in which switching transients were generated (Rogers *et al.*, 1995b).

(v) *Cellular effects*

The effects of magnetic fields on the function of the serotonin receptor, 5-HT1B, were studied in tissue samples of rat and guinea-pig brain and in Chinese hamster ovary cells transfected with the human form of the receptor. The tissue and cell samples were exposed to 50-Hz magnetic fields (0.01–10 mT) for 30 or 60 min before specific assays were performed. The authors observed an effect of the field on the

affinity constant of 5-HT1B receptors, which decreased (in a sigmoidal fashion at field intensities between 0.05 and 2 mT, with a threshold at 0.6 mT) when the response saturated. Functionally, the magnetic fields inhibited the action of a 5-HT1B agonist to produce cyclic adenosine monophosphate (cAMP) and also caused a change in the cellular activity of the receptors, as demonstrated by the inhibition of synaptosomal release of 5-HT1B receptors from rats, guinea-pigs and humans (Massot *et al.*, 2000). [The Working Group noted that it is unclear how these results relate to changes *in vivo*.]

4.2.5 *Behavioural effects*

Studies on the effects of ELF electric and magnetic fields on behaviour have included tests of:

— perception and detection;
— arousal and aversive activity responses; and
— learning and memory.

The studies of specialized response systems that operate in various animal species and are associated with exposure to electric and magnetic fields, such as communication of food location (in honeybees), electroreception systems (as found in certain fish species) and homing and navigation (found in several species of birds), are not discussed here.

(*a*) *Static fields*

Davis *et al*. (1984) observed that neither exposure of mice to a 60-Hz, 1.65-mT nor a 1.5-T static magnetic field resulted in any behavioural alterations in a passive avoidance learning test.

Exposure to a strong static magnetic field (600 mT) for 16 h per day for 14 weeks inhibited avoidance behaviour in rats (Nakagawa & Matsuda, 1988). A taste-aversion study was conducted in rats exposed to very high-intensity static magnetic fields (9.4-T magnet) for 30 min. The exposure was significantly associated with taste aversion (Nolte *et al.*, 1998) and the effect lasted throughout the eight days of post-exposure follow-up.

The effects of exposure of rats to static magnetic fields were also investigated in a maze test to assess alterations in learning ability. Newborn male and female rats exposed to a field of 0.5 T for 14 days postnatally showed no significant change in learning ability compared with sham-exposed controls when tested one month after exposure (Hong *et al.*, 1988).

If given a choice, rats preferred to stay out of a high-voltage static electric field when the field strength was ≥ 55 kV/m, whereas they showed no such aversion at field strengths ≤ 42.5 kV/m. Changes in the air concentrations of either positive or negative ions had no effect on aversive or non-aversive behaviour (Creim *et al.*, 1993).

(*b*) *ELF electric and magnetic fields*

(i) *Behavioural effects related to perception of fields*

Behavioural studies in several animal species provide evidence that the animals perceive the presence of electric and magnetic fields and suggest that electric fields may directly alter behaviour. A number of investigations have reported the threshold of detection of a vertical 60-Hz electric field to be in the range of 4–10 kV/m in rats (Stern *et al*., 1983). Male rats were trained to press a lever in the presence of the field and not to press in its absence. Control procedures showed that the behaviour required the rat to be in the electric field and that the behaviour was not controlled by any of several potentially confounding variables. Female rats, evaluated in a similar experimental signal-detection system showed comparable detection thresholds of 3–10 kV/m (Stern & Laties, 1985).

The thresholds for the perception of electric fields by animals other than rats have also been evaluated: they ranged from an average of 12 kV/m in baboons (with one animal perceiving a field as weak as 5 kV/m) (Orr *et al*., 1995b) to 35 kV/m in miniature swine, as determined by use of preference aversion measurements (Kaune *et al*., 1978). The perception threshold for mice was 25 kV/m, using arousal as the response indicator (Rosenberg *et al*., 1983), and that for chickens and pigeons was approximately the same (Graves *et al*., 1978; Graves, 1981). Human volunteers in certain postures were able to perceive a 9-kV/m electric field (Graham *et al*., 1987). It appears that changes in various environmental factors, such as relative humidity, can alter perception thresholds (Weigel & Lundstrom, 1987). Cutaneous sensory receptors that respond to 60-Hz electric fields have been identified in the cat paw (Weigel *et al*., 1987).

Detection of magnetic fields by animals is presumed to be quite different from that for perceiving electric fields and a wide divergence of results has been reported in various studies designed to evaluate detection of and response to magnetic fields by animals. By use of conditional suppression techniques to measure the response, rats were shown to be able to perceive the presence of a magnetic field as weak as 0.2 mT, with a 7–65-Hz frequency range (Smith *et al.*, 1994).

(ii) *Activity, aversion responses*

The arousal response of animals exposed to a stimulus is a less precise index of perception than the responses discussed above. Arousal and preference or avoidance responses have been determined at several field strengths for ELF electric and magnetic fields. Such responses were observed in mice exposed to 60-Hz electric fields. At 25, 50 and 100 kV/m the responses were transient and not sustained with prolonged or repeated exposure (Hackman & Graves, 1981; Rosenberg *et al*., 1981). When exposed to field strengths of 25 kV/m, rats preferred to spend their inactive period in the field (60 Hz). At 75–100 kV/m, they avoided exposure (Hjeresen *et al.*, 1980). To determine the strength of the aversion in rats, Creim *et al*. (1984) examined taste-aversion associated with exposure to electric fields. The animals showed no taste-aversion behaviour when exposed to electric fields up to 133 kV/m. Static fields

(approximately 75 kV/m) were also ineffective in producing taste aversion in rats (Creim *et al*., 1995).

There was no indication of aversive behaviour in mice exposed for 72 h to 1.65-mT static or 60-Hz magnetic fields (Davis *et al.*, 1984). These results were confirmed in other experiments showing a lack of aversive behaviour in rats exposed for 1 h to a 60-Hz, 3.03-mT magnetic field (Lovely *et al*., 1992). The internal body currents induced by this level of exposure were comparable to those from strong electric fields. Because aversion was not demonstrated with magnetic fields, but was observed with electric fields, these results suggest that the aversive behaviour is not due to internal body currents. One study, using special combinations of parallel static and alternating magnetic fields (at cyclotron resonance frequencies), reported a reduction in exploratory behaviour at much lower intensities of static fields (500 and 50 μT) (Zhadin *et al*., 1999).

At higher field intensities, both static (490 mT) and 50-Hz, 18-mT magnetic fields caused a decrease in irritability of rats after extended (2 h per day, 20 days) exposure (Trzeciak *et al*., 1993). No other significant behavioural effects were observed.

Swine exposed to 30-kV/m electric fields were reported to prefer the field during the day and to avoid exposure during the night (Hjeresen *et al*., 1982). At comparable exposures to 60-Hz, 30-kV/m electric fields, minor behavioural changes were observed in baboons, which appeared to be related to the animals' perception of the fields (Rogers *et al*., 1995c). Even at field strengths up to 65 kV/m, no aversive behaviour was noted in non-human primates, although some increase in social stress was induced in groups of baboons exposed to 60-kV/m electric fields (Easley *et al*., 1991). [The Working Group noted that only a few other behavioural changes have been reported after exposure of animals to electric fields up to 100 kV/m. Furthermore, the alterations that were seen in most studies were not persistent. Indeed, the animals quickly habituated to the presence of the electric field.]

(iii) *Neurobehavioural teratology*

Neurobehavioural teratology studies are reviewed in section 4.2.1.

(iv) *Learning, performance and memory*

As early as 1970, studies were conducted to examine the effects of ELF electric and magnetic fields on learning and performance. Macaques (*Macaca nemestrina*) exposed to weak electric fields of 4–10 Hz showed a disruption of the timing behaviour of an operant schedule response (Gavalas *et al*., 1970; Gavalas-Medici & Day-Magdaleno, 1976). Operant behaviour in baboons was studied after exposure to 30- and 60-kV/m electric fields, but other than an initial work stoppage in exposed animals, no effect on operant behaviour was observed (Rogers *et al*., 1995c). No effects were seen on response rate, number of errors or extinction of a simple task motivated by appetite (Rogers *et al*., 1995d). Social behaviour of baboons was not

affected by exposure to a 30-kV/m electric field for 12 h per day for 6 weeks (Coelho *et al*., 1991).

The spatial learning task is considered to reflect the 'working' or 'short-term' memory. Tests of the performance of rodents in a maze are the usual methods of assessing spatial learning during exposure. In adult male mice exposed for 45 min to a 50-Hz, 0.75-mT magnetic field immediately before testing in a radial arm maze, the rate of learning the task was significantly reduced, compared with unexposed controls, although the overall accuracy of the memory was not affected (Sienkiewicz *et al*., 1998). A similar test performed by rats exposed to 60-Hz, 0.75-mT magnetic fields showed a significant retardation of learning compared with sham-exposed controls. Treatment of the animals with the cholinergic agonist, physostigmine, before the exposure to the magnetic field reversed the field effect (Lai, 1996). Rats were also tested in a water maze to evaluate performance after exposure to a 1-mT magnetic field for 1 h. No differences between exposed and sham-exposed animals were observed in learning (ability to locate the platform); however, the swimming speed of the exposed rats was significantly lower than that of controls (Lai *et al*., 1998).

Thomas *et al*. (1986) and Liboff *et al*. (1989) reported that timing discrimination in rats was disrupted even by a very weak 60-Hz magnetic field of 26 μT. These results, however, could not be replicated in later studies conducted under the same exposure conditions (Stern et al., 1996).

Rats exposed overnight to a 7-Hz, ~ 50-nT magnetic field coupled with a known geomagnetic activity showed no significant differences in number of errors made or speed of acquisition of the learning task when compared with sham-exposed controls (McKay & Persinger, 1999).

Studies have also been conducted to evaluate learning, performance and memory in animals given operant tasks after exposure to combined electric and magnetic fields.

In a study in rats, Salzinger *et al*. (1990) exposed animals to 60-Hz fields of 30 kV/m and 100 μT. When the performance of complex operant tasks was tested at various times during the light/dark cycle, a slightly slower response was observed in exposed animals at one point in the cycle.

Groups of eight baboons were sham-exposed or exposed to 6-kV/m, 50-μT, and subsequently to 30-kV/m, 100-μT fields at 60 Hz (Orr *et al*., 1995a). In contrast to the effect seen with exposure to the electric field (30 kV/m) alone, there was no decrement of performance in the animals exposed to the combined fields. The authors suggest that the 100-μT magnetic field may have blocked the transient loss of performance. Other behavioural end-points were also unaffected in exposed baboons at these combinations of exposure to electric and magnetic fields (Coelho *et al*., 1995). Macaques (*Macaca nemestrina*) were exposed to combined 60-Hz fields of 3–30 kV/m and 10–90 μT for 18 h per day for three weeks. No changes were observed in the performance of the exposed animals in a food-motivated operant task compared with sham-exposed controls (Wolpaw *et al*., 1989).

There is clear evidence that animals can perceive electric fields at field strengths in the range of 3–10 kV/m and above. The ability to perceive ELF magnetic fields at low intensities is less well established, with both positive and negative indications of perception.

[The Working Group noted that both static and ELF magnetic fields have been shown to influence animals in learning and memory tasks. The data indicate that, for exposure to electric fields, aversive behaviour occurs above approximately 30–50 kV/m, depending on the animal species. For ELF magnetic fields, intensities of up to at least 18 mT do not appear to influence aversion. However, there have also been studies that showed no effects of exposure on either learning or memory acquisition. The results of a number of studies suggest that observation of field-related effects requires that exposure is closely coupled to testing in time, and may be more related to acquisition of the task or even to the state of arousal of the animal than to an effect on the memory itself. Because studies in this area show variable results, demonstrating both decreases in apparent learning ability and memory, and lack of any effect, it is difficult to draw firm conclusions as to the robustness of the effects of exposure to magnetic fields on learning.]

4.3 Effects of ELF electric and magnetic fields on bone healing[1]

In some situations the interaction of electric and magnetic fields with biological systems may be beneficial and lead to new medical applications. Examples include nuclear magnetic resonance imaging (MRI), electromagnetically induced hyperthermia, and bone healing with pulsed electromagnetic fields. This section will briefly discuss the evidence for the beneficial effects of exposure to electric and magnetic fields on bone healing in humans. Similar studies in animals and in-vitro experiments dealing with this topic have been reviewed in detail elsewhere (Portier & Wolfe, 1998) and will not be discussed here.

The therapeutic effects of specific low-energy, time-varying magnetic fields (pulsed electromagnetic fields, PEMF) on bone healing were first documented in 1973. These effects are based on the generation of electrical currents within the bone tissue by magnetic induction. These currents enhance the activity of bone-forming cells, the osteoblasts (Cane *et al.*, 1993). Initially, this form of treatment with athermal energy was used mainly for patients with juvenile or adult non-unions, i.e. bone fractures showing no sign of union nine months after injury, despite the usual forms of surgical treatment, including bone grafting. The biological effectiveness of PEMF therapy in augmenting bone healing has been confirmed by several double-blind and placebo-controlled prospective studies, and supported by laboratory studies (for an early review, see Bassett 1989).

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[1] For the sake of completeness, this section was added by the IARC secretariat after the Working Group Meeting.

A group of 125 patients with non-united fractures of the tibial diaphysis were treated for >10h/day with PEMF (15-Hz pulse burst; 1.5-mT peak flux density; 25-μs decay time; 4-kHz pulse repeat rate; 5-ms burst duration). This treatment resulted in an estimated electric field pulse of 0.1–0.2 V/m in the bone tissue. Healing of the fracture was observed in 87% of the patients who required an average treatment duration of 5.2 months (range, 2–22 months). Failure of the therapy was attributed by the authors to inadequate immobilization of the fractured bone, separation of opposing fractured bone surfaces by more than 1 cm, exposure for less than 10 h/day, or incorrect positioning of the induction coils (Bassett *et al.*, 1981).

A double-blind, randomized, placebo-controlled trial of magnetic field therapy was conducted in 16 patients with tibia fractures that had not healed for at least one year. All patients received full leg plasters and were divided into a treatment group (9 patients; average age, 38 years) and a placebo group (7 patients; average age, 29 years). The patients were instructed to use PEMF stimulators — active or inactive — for 12–16 h/day, with coils designed to fit around the cast of each patient. The active devices produced a 1.5-mT peak intensity, 5-ms burst waveform repeated at 15 Hz. At 24 weeks, the fractures in 5/7 patients in the placebo group and 5/9 patients in the treatment group had healed. The authors concluded that magnetic field therapy is not more effective than the traditional treatment of these fractures (Barker *et al.*, 1984).

A group of 45 patients with tibial shaft fractures were included, over a period of 6 years, in a double-blind multi-centre trial to assess the effect of exposure to PEMF on bone fracture healing. The fractures had not shown union for 16–32 weeks, and some were characterized by severe displacement, angulation or the presence of injury to soft tissue and skin. Plaster immobilization was used in all patients (mean age, 35 years), 20 of whom received active electromagnetic stimulation (15-Hz pulse burst; 200-μs pulse duration; 25-μs decay time; peak flux density not reported). The other 25 patients (mean age, 45 years; significantly different from that of the treatment group) served as controls and used non-functioning stimulators. Treatment continued for 12 weeks, for 12 h/day. In the treatment group, union was observed in five cases, progress to union in five patients, but no progress was reported in 10 patients. In the control group the numbers of patients were one, one and 23, respectively ($p = 0.002$) (Sharrard, 1990).

In two randomized placebo-controlled clinical trials with 32 and 37 patients, respectively, treatment with pulsed magnetic fields (1.8 mT; repeat frequency, 75 Hz; rise time, 1.3 ms; estimated peak intensity of the induced electric field, 50 mV/m) for 8 h/day for up to 90 days induced a significant increase in trabecular bridging after surgical bone transection (Borsalino *et al.*, 1988; Mammi *et al.*, 1993).

A randomized double-blind prospective study was conducted in 195 patients who underwent lumbar interbody fusion, a surgical procedure aimed at connecting adjacent vertebrae. The study comprised 98 patients exposed to 15-Hz pulse-burst signals of 1.5 mT (rise time, 25 μs; repeat rate, 4 kHz; burst duration, 5 ms) and 97 patients in the placebo group. Both groups were asked to wear a brace for 8 h/day. Fusion was

observed in 60 of 65 patients (92%) in the treatment group and in 63 of 97 (65%) patients carrying a placebo device ($p < 0.005$). The success rate in 33 patients who used the active brace for less than 4 h/day was similar to that of the placebo group (Mooney, 1990).

Another double-blind clinical trial was conducted in patients undergoing limb-lengthening surgery, which involves transection of the bone, distraction of the bone ends, and regeneration of bone tissue in the distraction gap. Patients were asked to wear the induction devices — active or placebo — for 4 h/day for up to 12 months. Exposure conditions to the pulsed magnetic fields were similar to those described in the previous study (Mooney, 1990). Bone densities were measured by X-ray analysis at the mid-point of the gap and at the proximal and distal ends. No difference between the treatment and placebo groups was observed either in limb-lengthening rate or in bone density at the distraction gap. However, there was a significant increase of bone density in the proximal segment in the field-exposed group, and a significant reduction of bone loss at the distal side (Eyres *et al.*, 1996).

A recent clinical trial used low-amplitude PEMF on 19 patients with non-union or delayed union of the long bones. The stimulator device produced 0.3-ms pulses repeated at 80 Hz, with maximum magnetic fields of 0.01–0.1 mT, i.e. considerably weaker than in previous studies. Stimulation was applied for 9–12 h/day until mobility at the fracture site had disappeared. Among the 13 patients (age range, 9–90 years; period since injury 8–108 weeks, average 41.3 weeks) who completed the treatment, 11 had successfully healed bones, after treatment periods of 4–27 weeks. The two unsuccessful cases had bone gaps greater than 1 cm after removal of dead bone after infection. The authors concluded that weak magnetic fields may be effective in stimulating bone healing (Satter-Syed *et al.*, 1999).

A recent review discussed studies in which magnetic fields were applied to promote bone-healing, to treat osteoarthritis and inflammatory diseases of the musculoskeletal system, to alleviate pain, to enhance healing of ulcers and to reduce spasticity. The action of magnetic fields on bone healing and pain alleviation was confirmed in most of the trials. In the treatment of other disorders the results have been contradictory. Application times varied between 15 minutes and 24 hours per day for three weeks up to 18 months. There seems to be a relationship between longer daily application time and positive effects, particularly in bone-healing. Of the 12 well-controlled studies dealing with the application of pulsed magnetic fields on bone healing, 11 reported a more rapid and improved healing process, compared to placebo controls. In all these studies, a treatment duration of 8–12 hours per day appeared to be required to produce the beneficial effect. It was noted that optimal dosimetry for this type of therapy has yet to be established (Quittan *et al*., 2000).

4.4 Genetic and related effects

4.4.1 *Genotoxic effects*

(*a*) *Studies in humans*

(i) *Static magnetic fields*

No data were available to the Working Group.

(ii) *ELF electric and magnetic fields*

Several studies were carried out to investigate the clastogenic effects of exposure to power-frequency electric and magnetic fields and transient electric currents.

Chromosome analyses were performed on lymphocytes from 32 workers occupationally exposed for more than 20 years to 50-Hz electric and magnetic fields in 380-kV switchyards. Comparison with a control group of 22 workers of similar age and occupation, who had not been exposed to electric or magnetic fields, showed that neither the numbers of structural chromosomal changes nor the frequencies of sister chromatid exchange were increased (Bauchinger *et al.*, 1981).

Chromosomal aberrations in lymphocytes from three groups of welders were examined. The technology used by one group of welders gave rise to elevated concentrations of nickel in their serum and urine. Although all three groups were exposed to essentially the same electrical discharges, only the welders with the higher concentrations of nickel had increased chromosomal aberrations in their lymphocytes. There were no correlations between the number of aberrations and the concentration of nickel in the serum or the duration of occupational exposure, but correlations were found with the number of cigarettes smoked. It was concluded that certain welding processes produce fumes that seem to have effects on chromosomes, but that fields from welding *per se* do not seem to cause increased aberrations (Elias *et al.*, 1989).

Lymphocytes from the peripheral blood of 20 switchyard workers (9 smokers, 11 non-smokers) were assayed for chromosomal anomalies. The rates of chromatid and chromosome breaks were found to be significantly increased compared to those in lymphocytes from 17 control subjects (7 smokers, 10 non-smokers) (Nordenson *et al.*, 1984).

In a follow-up to the previous study, data were reported on 38 employees of electric power companies, 19 of whom worked on the repair and maintenance of circuit breakers and disconnectors in 400-kV substations. The other 19 served as controls and were exposed only to normal environmental electric and magnetic fields. Coded blood samples were analysed for the presence of chromosomal aberrations, sister chromatid exchanges (SCE), and cells with micronuclei. Compared with the control group, the exposed subjects showed a statistically significant increase in chromosomal aberrations and cells with micronuclei, but not in the frequency of SCE. Because similar results were obtained in studies of lymphocytes exposed *in vitro* to transient electric currents (spark discharges), the increase in chromosomal damage in substation workers may be

associated with exposure to transient electric currents during work (Nordenson *et al.*, 1988).

Chromosomal aberrations, SCEs, replication indices and micronuclei were analysed in lymphocytes from the peripheral blood of 27 non-smoking power linemen who had considerable long-term exposure to 50-Hz electric and magnetic fields. An equal number of non-smoking telephone linemen were matched pair-wise with the exposed workers for age and geographical region, and served as controls. No differences between the groups were observed with respect to SCEs, replication indices or micronuclei. The overall frequency of chromosomal aberrations was higher in the exposed workers than in the controls, but the difference was not significant. However, the mean rate of lymphocytes with chromatid-type breaks was significantly higher in the power linemen than in the reference group. The excess of aberrant cells was observed mainly in lymphocytes from power linemen who had smoked earlier in their life. Although the interpretation is complicated by the confounding effect of having been a smoker, these results suggest that exposure to 50-Hz electric and magnetic fields is associated with a slight increase in chromatid breaks (Valjus *et al.*, 1993).

Thirteen workers in a high-voltage laboratory and 20 controls participated in a cross-sectional, matched-pairs study of cytogenetic damage. During cable testing the workers were exposed to static, alternating (50 Hz), or pulsed electric and magnetic fields. The magnetic field strength was normally 5–10 μT, but was occasionally much higher. Chromosomal aberrations, SCE and aneuploidy were studied in lymphocytes from the peripheral blood of exposed workers and controls. In addition, chromosomal aberrations were investigated in lymphocyte cultures treated with hydroxyurea and caffeine, to inhibit DNA synthesis and repair. Among seven laboratory workers (all smokers) the mean number of chromosome breaks/200 cells was 2.3, as compared with 0.7 for controls matched for job, age and smoking habits. The comparable figures for the cultures treated with hydroxyurea and caffeine were 12.0 and 6.0, respectively. No field-related increase was detected in non-smokers by either method. The other genetic parameters did not differ between the exposed workers and the controls (Skyberg *et al.*, 1993).

A cytogenetic analysis was carried out on cultured (48 h) peripheral lymphocytes of Swedish train drivers exposed to relatively strong magnetic fields up to > 100 μT. A pilot study with lymphocytes from 18 train drivers indicated a significant difference in the frequency of cells with chromosomal aberrations (gaps included or excluded) in comparison with seven concurrent controls (train dispatchers) and a control group of 16 office workers. The frequencies of cells with chromosome-type aberrations (excluding gaps) were about four times higher in train drivers than in office workers ($p < 0.01$) and dispatchers ($p < 0.05$). Seventy-eight percent of the train drivers had at least one cell with chromosome-type aberrations per 100 compared with 29% for the dispatchers and 31% for the office workers. In a follow-up study on a group of 30 train drivers, half of the cytogenetic slides from each subject were examined in one laboratory and the remainder was analysed in another; a statistical analysis showed no difference in results

between laboratories, so the data were pooled. The results showed an increase ($p < 0.05$) in the frequency of cells with chromosome-type aberrations (gaps excluded) in the train drivers compared with that in a control group of 30 policemen. Sixty percent of the train drivers had one or more cells per 100 cells with chromosome-type aberrations compared with 30% among the policemen. These results support the hypothesis that exposure to magnetic fields at mean intensities of 2–15 μT can induce chromosomal damage *in vivo* (Nordenson *et al.*, 2001).

A cross-sectional study was carried out in a Norwegian transformer factory of 24 workers exposed to electric and magnetic fields and mineral oil, and 24 matched controls. The exposure group included employees in the high-voltage laboratory and in the generator-welding department. Electric and magnetic fields and oil mist and vapour were measured. Blood lymphocytes were cultured and analysed for chromosomal aberrations. In addition to conventional cultures, the lymphocytes were also treated with hydroxyurea and caffeine to inhibit subsequent DNA synthesis and repair. The results of the conventional lymphocyte cultures were similar in the exposure group and the controls for all cytogenetic parameters. In the cultures in which DNA synthesis and repair were inhibited, the cytogenetic parameters of the lymphocytes from generator welders did not differ from those of the controls, whereas in lymphocytes from workers in the high-voltage laboratory, the numbers of chromatid breaks, chromosome breaks and aberrant cells were significantly increased compared with control values. More years of exposure and smoking increased the risk of aberrations. No increase in cytogenetic damage in exposed workers compared to controls was detected with the conventional lymphocyte assay. In repair-inhibited cultures, however, there were indications that electric and magnetic fields in combination with exposure to mineral oil may produce chromosomal aberrations (Skyberg *et al.*, 2001).

(*b*) *Studies in animals*

(i) *Static magnetic fields*

Wing spot tests were performed in *Drosophila melanogaster* to examine the possible mutagenic activity of a static magnetic field. A DNA repair-defective mutation was introduced into the conventional test system to enhance the frequency of the mutant spots. Third instar larvae were exposed to a horizontal 5-T static magnetic field for 24 h. After moulting, wings were examined under a microscope to detect hair spots (large single and twin spots) with mutant morphology, indicative of somatic recombination. The exposure caused a statistically significant enhancement of somatic recombination compared with the unexposed control. This enhancement was suppressed to the control level by treatment with vitamin E, a non-specific antioxidant. Enhancement of non-disjunction, terminal deletions and gene mutations was not detected (Koana *et al.*, 1997). [The Working Group noted that there is limited information on the genetic effects of static magnetic fields.]

(ii) *ELF electric and magnetic fields*

Cytogenetic effects, DNA breaks, DNA cross-links

The effect of long-term exposure to a magnetic field on subsequent cell proliferation and the frequency of SCE was examined in the peripheral lymphocytes of female Wistar rats following in-vivo exposure to a 50-Hz, 30-mT magnetic field for 7 or 28 days. As a positive control, another group of rats was treated with cyclophosphamide. The magnetic field influenced neither the frequency of SCE nor the proliferation characteristics of cultured peripheral lymphocytes (measured as mitotic indices and proliferation index) (Zwingelberg *et al.*, 1993).

The acute effect of magnetic fields on DNA integrity was examined in male Sprague-Dawley rats (age, 2–3 months; weight, 250–300 g), which were exposed in the Helmholtz coil system to a 60-Hz magnetic field at flux densities of 0.1, 0.25 and 0.5 mT for 2 h. Four hours after exposure, the rats were killed and DNA single-strand and double-strand breaks were assayed in brain cells by single-cell gel electrophoresis ('comet' assay) at neutral and alkaline pH. A significant increase in DNA single-strand breaks was observed in all cases, and the effect was dose-dependent. No significant effect on DNA double-strand breaks was observed after exposure to the 0.1-mT magnetic field, but a significant increase was seen at flux densities of 0.25 and 0.5 mT (Lai & Singh, 1997a).

Studies were conducted to determine whether treatment with melatonin and the spin-trap compound *N*-*t*-butyl-α-phenylnitrone could block the effect of magnetic fields on brain-cell DNA. Rats were injected with melatonin (1 mg/kg bw, subcutaneously) or *N*-*t*-butyl-α-phenylnitrone (100 mg/kg bw, intraperitoneally) immediately before and after two hours of exposure to a 60-Hz, 0.5-mT magnetic field. Brain cells were assayed by single-cell gel electrophoresis and both treatments were found to block induction by the magnetic field of DNA single- and double-strand breaks. Since melatonin and *N*-*t*-butyl-α-phenylnitrone are efficient scavengers of free radicals, the authors inferred that free radicals may play a role in DNA damage induced by magnetic fields (Lai & Singh, 1997b).

In the same laboratory, DNA–protein and DNA–DNA cross-links were studied by use of the single-cell gel electrophoresis assay. Male Sprague-Dawley rats (age, 2–3 months; weight, 250–300 g) were exposed in the Helmholtz coil system to a sinusoidal 60-Hz, 0.5-mT magnetic field for 2 h. Rats were killed 4 h after exposure. Most of the increase in DNA migration induced by the magnetic field was observed only after treatment with proteinase-K, suggesting the presence of DNA–protein cross-links. In addition, when brain cells from control rats were exposed to X-rays, an increase in DNA migration was observed, the extent of which was independent of treatment with proteinase-K. However, the X-ray-induced increase in DNA migration was retarded in cells from animals exposed to magnetic fields even after treatment with proteinase-K, suggesting that DNA–DNA cross-links were also induced by the field. The effects of magnetic fields were also compared with those of mitomycin C, a known inducer of

DNA cross-links. The pattern of effects was similar with the two agents (Singh & Lai, 1998).

Degradation of DNA was measured by single-cell gel electrophoresis in brain cells of CBA mice exposed *in vivo* continuously to 50-Hz, 0.5-mT magnetic fields for 2 h, 5 days or 14 days. No differences between the groups exposed for 2 h and 5 days and controls were observed. However, in the group exposed to the magnetic fields for 14 days, a significantly extended brain cell DNA migration was observed ($p < 0.05$) (Svedenstål *et al*, 1999a).

CBA mice were exposed outdoors to 50-Hz electromagnetic fields, with a flux density of about 8 μT, generated by a 220-kV transmission line. Possible genotoxic effects as well as effects on body weight, leukocyte and erythrocyte counts, and the level of ornithine decarboxylase activity in spleen and testis were determined after 11, 20 and 32 days of exposure. Ornithine decarboxylase is an enzyme involved in the synthesis of putrescine from ornithine, which is one of the polyamine synthesis pathways. DNA degradation was studied in brain cells by single-cell gel electrophoresis. After 32 days of exposure, a highly significant increase of the tail:head ratio of the comets was observed ($p < 0.001$), indicative of DNA damage. A decreased number of mononuclear leukocytes ($p < 0.05$) was observed in mice exposed for 20 days (Svedenstål *et al*, 1999b). [The Working Group noted that the single-cell gel electrophoresis assay following in-vivo exposure is particularly protocol-dependent, specifically with respect to the method of killing the animals and the treatment of tissue samples between exposure of the animal and analysis of the tissues.]

Dominant lethal mutations

Sexually mature, male C3H/He mice, aged 8–10 weeks at the beginning of a study to determine the induction of dominant lethal mutations, were exposed continuously for two weeks to a vertical, 50-Hz, 20-kV/m electric field or sham-exposed. Current densities induced in the testes were estimated to be approximately 100 $\mu A/m^2$. After exposure, each male was mated weekly with two different female mice for eight weeks. In this way, female mice were inseminated with sperm that had been exposed to the electric field at different stages of the spermatogenic cycle. Another group of male mice was exposed to 169-keV X-rays for about 150 min and served as a positive control. In this group, the estimated dose to the testis was 1.5 Gy. Whereas the positive controls gave clear evidence of mutagenesis, no significant changes related to exposure to an electric field were observed in fertilization rates or in survival of embryos before or after implantation (Kowalczuk & Saunders, 1990).

In a second assay of dominant lethal mutation a total of 42 male mice were exposed for eight weeks to a 50-Hz, 10-mT sinusoidal magnetic field. A group of 47 males was used as simultaneous cage controls. Each male was subsequently mated with two females on weeks 1, 3, 5, 7 and 9 post-exposure. The numbers of gestating females, corpora lutea, and live and dead implants were recorded. Multiple logistic regression

analyses were used to examine the effects of exposure on fertilization rate, pre-implantation survival and post-implantation survival. There were no differences in overall response between the exposed and control groups, nor was any significant effect of exposure seen at any number of weeks after exposure. Thus, exposure to power-frequency magnetic fields at 10 mT for the approximate period of spermatogenesis did not appear to induce dominant lethal mutation in the germ cells of male mice (Kowalczuk *et al*., 1995). [The Working Group noted that the dominant lethal mutation assay is not sufficiently sensitive to allow detection of weak mutagens.]

(*c*) *In-vitro studies*

(i) *Static magnetic fields*

Micronucleus formation

The formation of micronuclei occurs when a chromosome or a chromosome fragment is released from the nucleus as a result of strand breakage or disturbance of spindle function during mitosis.

The effects of exposure to a 4.7-T homogeneous static magnetic field on the frequency of micronuclei induced in cultured CHL/IU cells by mitomycin C were studied. Simultaneous exposure to the magnetic field and mitomycin C for 6 h significantly decreased the frequency of mitomycin C-induced micronucleated cells analysed after post-treatment culture periods of 18, 42, 54 and 66 h. In both field-exposed and control groups, the highest frequency of mitomycin C-induced micronucleated cells was observed 42 h after treatment; the frequency decreased gradually after this time (Okonogi *et al*., 1996).

Mutation

The possible mutagenic and co-mutagenic effects of strong static magnetic fields were examined in a bacterial mutagenicity test. A super-conducting magnet was used to generate a homogeneous static magnetic field with a flux density of up to 5 T. Exposure to this field produced no mutations in four strains of *Salmonella typhimurium* (TA100, TA1535, TA1537 and TA98) or in *Escherichia coli WP2 uvrA* either using the pre-incubation method or in the plate-incorporation assay. In the co-mutagenicity test, *E. coli WP2 uvrA* cells were treated with various chemical mutagens and simultaneously exposed to a 2-T or a 5-T static magnetic field. The mutation rate in the group exposed to the magnetic field was significantly higher than in the unexposed group when cells were treated with six different alkylating agents. Exposure to the magnetic field did not affect the mutagenicity of 2-aminoanthracene, 9-aminoacridine, N^4-aminocytidine or 2-acetoamidofluorene (Ikehata *et al*., 1999).

(ii) *ELF electric and magnetic fields*

Chromosomal aberrations and sister chromatid exchange

Many researchers have determined the frequency of chromosomal aberrations and sister chromatid exchange in response to exposure to ELF electric and magnetic fields. Several studies with peripheral human blood lymphocytes have been reported in which exposure *in vitro* to 50- or 60-Hz magnetic fields (30 μT–7.5 mT) caused no increase in the frequency of chromosomal aberrations or sister chromatid exchanges (Cohen *et al.*, 1986a,b; Rosenthal & Obe, 1989; Antonopoulos *et al.*, 1995; Paile *et al.*, 1995). However, 72 hours of continuous in-vitro exposure to 10-ms pulses of a magnetic field (50 Hz, 1.05 mT) caused a significant increase in the frequency of chromosomal aberrations and sister chromatid exchanges in the lymphocytes from three male donors (Khalil & Qassem, 1991).

In-vitro exposure of human peripheral lymphocytes to a 50-Hz electric current with a current density of 1 mA/cm^2 did not induce any chromosome damage. Exposure to 10 spark discharge pulses (duration, 3 μs) with a peak field strength in the samples of 3.5 kV/cm, however, resulted in chromosome breaks at a frequency similar to that induced in lymphocytes *in vitro* by 0.75 Gy ionizing radiation (Nordenson *et al.*, 1984).

Lymphocytes from human peripheral blood were exposed for 48 h to 50-Hz magnetic fields (62.8, 80, 88.4, 504, 1061, 1750 and 2500 μT) and examined for cytogenetic effects. No significant changes in chromosomal aberration or sister chromatid exchange frequencies were observed. Combined treatments with mutagens (mitomycin C or X-rays) and 50-Hz magnetic fields did not reveal any significant synergistic, potentiating or antagonistic effects between magnetic fields and these mutagens (Maes *et al.*, 2000).

Exposure of Chinese hamster V-79 cells to 25-μs pulses of a magnetic field (0.18–2.5 mT) repeated at 100 Hz for 24 h did not increase sister chromatid exchanges (Takahashi *et al.*, 1987).

A significant increase in sister chromatid exchanges was found in mouse m5S cells exposed for 42 h to a strong ELF magnetic field (50 Hz, 400 mT) (Yaguchi *et al.*, 1999). In contrast, exposure to magnetic fields ≤ 50 mT did not cause any increase in the frequency of sister chromatid exchange in these cells. Chromosomal aberration analysis revealed an increased frequency of chromatid-type aberrations such as gaps in response to exposure to magnetic fields with flux densities of 50 mT and higher (Yaguchi *et al.*, 2000). Intermittent (15 s on, 15 s off) exposure of human amniotic cells to a 50-Hz, 30-μT magnetic field over 72 h doubled the frequency of chromosomal aberrations including gaps ($p < 0.05$). However, increased frequencies of chromosomal aberrations were not observed after continuous exposure to a 300-μT magnetic field (Nordenson *et al.*, 1994). When mouse m5S cells were exposed to a 60-Hz, 50-mT or a 50-Hz, 400-mT magnetic field after pre-exposure to X-rays (3 Gy) or mitomycin C (1 μM), chromatid-type aberrations were enhanced by the ELF magnetic field (Yaguchi *et al.*, 2000). Combined exposure of lymphocytes from human peripheral blood to an ELF

magnetic field (60 Hz, 1.4 mT) and ionizing radiation (3 Gy) resulted in a higher frequency of tetraploid cells than that produced by ionizing radiation alone (Hintenlang, 1993).

DNA strand breaks

Various studies in which cultured mammalian cells were exposed to ELF magnetic fields (0.2 μT–5 mT) found no induction of DNA single-strand breaks (Reese *et al*., 1988; Fiorani *et al*., 1992; Fairbairn & O'Neill, 1994; Cantoni *et al*., 1996). In contrast to the results of an in-vivo exposure study in rats (Lai & Singh, 1997a), there was no significant increase in DNA strand breaks, as measured by single-cell gel electrophoresis, in cultured MO54 human brain tumour cells exposed for 30 min to strong 50- or 60-Hz fields (5–400 mT) (Miyakoshi *et al*., 2000a).

In a study examining the combined effects of ELF electric and magnetic fields and oxidative stress, human Raji cells were treated with hydrogen peroxide and simultaneously exposed to a pulsed field with a peak amplitude of 5 mT (pulse duration, 3 ms; pulse frequency, 50 Hz). Analysis of these cells by the single-cell gel electrophoresis assay showed no effect of the electric and magnetic field on the number of DNA single-strand breaks induced by hydrogen peroxide (Fairbairn & O'Neill, 1994). Similarly, exposure to 50-Hz fields (20-kV/m electric, 0.2-mT magnetic, or a combination of these) had no influence on DNA single-strand breaks (measured by alkaline elution) in Chinese hamster ovary, CCRF-CEM and McCoy's cells pre-treated with methylmethane sulfonate, potassium chromate, ultraviolet radiation or hydrogen peroxide (Cantoni *et al*., 1995, 1996).

Three studies reported on the modifying effects of exposure to ELF electric and magnetic fields on the repair of DNA damage induced in human lymphocytes by ionizing radiation. Two of the studies found no inhibition of the repair of DNA damage induced by ionizing radiation (100 Gy or 5 Gy) after post-irradiation exposure of the cells to pulsed magnetic fields (repetition rate, 50 Hz; peak intensity, 2.5 mT) or to 60-Hz magnetic or electric fields, as judged by indices of DNA rejoining and unscheduled DNA synthesis (Cossarizza *et al*., 1989a; Frazier *et al*., 1990). However, when human glioma MO54 cells were exposed to 50- and 400-mT magnetic fields for 30 min after X-ray irradiation at 4 °C (to inhibit enzymatic strand rejoining), a slight but significant increase in the number of DNA strand breaks was observed (Miyakoshi *et al*., 2000a).

Lymphocytes from male Wistar rats were exposed for 3 h to either static or 50-Hz magnetic fields at 7 mT. In some cases, hydrogen peroxide or $FeCl_2$ was added to the medium. DNA damage (single-strand breaks and alkali-labile sites) were detected using the single-cell gel electrophoresis assay. Exposure to the static or 50-Hz fields did not produce any detectable DNA damage, nor did hydrogen peroxide or $FeCl_2$ alone. However, when lymphocytes were incubated with $FeCl_2$ and simultaneously exposed to 7-mT magnetic fields, the number of damaged cells was significantly

increased and reached about 20% after exposure to static and 15% after exposure to 50-Hz magnetic fields (Zmyslony *et al*., 2000).

Micronucleus formation

Micronucleus formation was examined in human lymphocytes exposed to 50-Hz sinusoidal electric fields at 0.5, 2, 5 and 10 kV/m in air. No difference was found between the frequency of micronuclei in cultures exposed to the electric fields at any of the intensities tested and that in unexposed control cultures (Scarfi *et al*., 1993). When mitomycin C was added to the cultures, the frequency of micronuclei increased significantly, but no difference was found between field-exposed and unexposed cultures. Many studies have found no effect of sinusoidal and pulsed power-frequency fields of 30 μT to 2.5 mT on micronucleus formation (Saalman *et al*., 1991; Scarfi *et al*., 1991, 1994; Lagroye & Poncy, 1997; Scarfi *et al*., 1999). In contrast, two studies have shown positive effects. A statistically significant increase in the frequency of micronuclei in human squamous-cell carcinoma SCL II cells was observed after continuous exposure to 50-Hz magnetic fields (0.8 and 1.0 mT) for 48 h and 72 h (Simkó *et al*., 1998a). However, in a non-transformed cell line cultured from human amniotic fluid used in the same study, there was no increase in the number of micronuclei induced by similar exposure to an ELF magnetic field. Another group reported an increase in the number of micronuclei in the same cell line after horizontal exposure to a 50-Hz, 1-mT magnetic field (Simkó *et al*., 1998b). Exposure to a 50-Hz, 100-μT magnetic field for 24 h after 6 Gy γ-radiation caused a significant increase in the number of binucleated cells with micronuclei compared to exposure to γ-radiation alone (Lagroye & Poncy, 1997).

Scarfi *et al.* (1997) reported an increase in the number of micronuclei in human lymphocytes from donors with Turner syndrome when the cells were exposed for 72 h to magnetic fields pulsed at 50 Hz (peak flux density was 2.5 mT, rise time 1.2 ms, pulse width ~ 2 ms, rate of change of 1.0 T/s, and the induced electric field was estimated to be 0.05 V/m). However, they observed no change in the number of micronuclei seen in lymphocytes from either normal donors or those with Turner syndrome when these cells were exposed to sinusoidal 50-Hz magnetic fields at 1 mT for 72 h (Scarfi *et al.*, 1996).

Mutation

The Ames assay using different strains of *Salmonella typhimurium* (TA100, TA98, TA97a and TA1102) revealed no effect of exposure to ELF magnetic fields (60, 600 and 6000 Hz; 0.3 mT, for 48 h) on mutation frequency (Morandi *et al*., 1996). Juutilainen and Liimatainen (1986) found no increase of mutation in *S. typhimurium* strains TA100 and TA98 exposed to 100-Hz magnetic fields (0.13, 1.3 or 130 μT), alone or in combination with the chemical mutagens 4-nitro-*ortho*-phenylenediamine or sodium azide. Exposure of Chinese hamster cells to ELF magnetic fields for seven

days (1 μT; 50 Hz) did not cause a significant increase in the mutation frequency of the *Hprt* gene encoding the enzyme hypoxanthine-guanine phosphoribosyl transferase (Nafziger *et al*., 1993). However, exposure of human melanoma MeWo cells to a strong magnetic field (50 Hz, 400 mT) resulted in an increase in the number of mutations of this gene. When the MeWo cells were exposed to the magnetic field in an annular culture plate (diameter, 15 cm), the frequency of *HPRT* mutations increased from the centre of the plate towards the edge, indicating increased mutation frequency with increasing current density. Under conditions of inhibited DNA synthesis, no induction of mutation was observed. Specifically, there was increased mutation induction during the S phase of the cell cycle (Miyakoshi *et al*., 1996a, 1997). In a study of exposure of *Drosophila melanogaster* larvae to an ELF magnetic field (20 mT) using an annular plate, the frequency of somatic mutations increased as a function of induced current (Koana *et al*., 2001). In a direct examination of the effects of electric fields, a 10-h exposure to a 60-Hz, 10-V/m electric field induced about twice as many *Hprt* gene mutations as in sham-exposed larvae (Ding *et al*., 2001).

Exposure to a strong magnetic field (50 Hz, 400 mT) induced mutations in the *HPRT* gene of *p53*-deficient human osteosarcoma cells. These mutations were suppressed by expression of the wild-type *p53* gene introduced on a plasmid (Miyakoshi *et al*., 1998a).

In a study of the mutagenic effects of ELF fields, continuous exposure to a 60-Hz, 5-mT magnetic field for six weeks did not significantly increase the frequency of *Hprt* mutations in CHO-K1 cells (Miyakoshi *et al*., 1999).

Concomitant exposure to an ELF magnetic field (60 Hz, 3 mT) and menadione, a compound that induces the formation of free radicals, or *N*-methyl-*N*-nitrosourea, an alkylating agent, did not influence the mutation rate in the *E. coli lacI* target gene in *lacI*-transgenic rat embryo fibroblasts (Suri *et al*., 1996).

Two studies on mutation induction by combined exposure to ionizing radiation and EMF fields showed that the frequency of mutations in the *Hprt* gene induced by X-rays (3 Gy) in CHO-K1 cells was significantly increased by exposure to 5-mT ELF magnetic fields during 1–6 weeks following X-ray irradiation (Miyakoshi *et al*., 1999; Walleczek *et al*., 1999). In a third study, human glioma cells were exposed for eight days to a 60-Hz, 5-mT magnetic field following X-ray irradiation (4 Gy). The frequency of *HPRT* gene mutation was increased approximately fourfold, compared to that induced by X-rays alone (Ding *et al*., 2001). These results show that ELF electric and magnetic fields can modulate the effects of ionizing radiation.

4.4.2 *Effects relevant to non-genotoxic carcinogenesis*

(*a*) *In-vivo studies*

(i) *ELF electric and magnetic fields*

The influence of a 50-Hz magnetic field and simulated solar radiation on ornithine decarboxylase (ODC) activity and polyamines was studied in mouse epidermis. Chronic exposure of mice to combined magnetic fields and simulated solar radiation

had no persistent effects on ODC activity or polyamines in comparison with animals exposed to ultraviolet radiation alone, although the same magnetic field treatment had previously been found to accelerate skin tumour development (Kumlin *et al*, 1998b). In an acute 24-h experiment, elevation of putrescine and down-regulation of ODC activity were observed in animals exposed to a 50-Hz, 100-μT magnetic field. No effect was seen 24 h after exposure to simulated solar radiation alone (Kumlin *et al*, 1998a).

A biomarker study was conducted during an ongoing initiation–promotion assay with SENCAR mice (see section 3, Sasser *et al.*, 1998). The study focused on early biochemical changes in epidermal cells associated with skin tumour promotion, including labelling index, ODC activity, protein kinase C activity and epidermal thickness, which were obtained from animals that had been DMBA-initiated and (12-*O*-tetradecanoylphorbol 13-acetate)-promoted and subsequently exposed to a 60-Hz, 2-mT magnetic field for 6 h per day for 5 days per week. No differences were reported for ODC activity or epidermal thickness, but a significant increase in down-regulation of the activity of protein kinase C was seen in the field-exposed mice at certain times during the promotion phase (DiGiovanni *et al*., 1999). [The Working Group noted that ambient levels of protein kinase C activity in the pilot experiment were substantially lower (by a factor of 10).] The authors concluded that the inability of the 60-Hz, 2-mT magnetic field to alter early biomarkers provides further evidence for the lack of a promotional or co-promotional effect of magnetic fields seen in the tumour development assay (Sasser *et al*., 1998).

Female rats were exposed to a 50-Hz, 50-μT magnetic field for a period of six weeks, in combination with oral administration of the chemical carcinogen DMBA. In control rats, exposure to the magnetic field alone resulted in an approximate doubling of ODC activity in mammary tissue, and a significant increase in ODC activity in the spleen, but not in the liver, small intestine, bone marrow or ear skin. Combined treatment with the magnetic field and DMBA was not more effective in increasing ODC activity than treatment with DMBA alone, except in liver tissue (Mevissen *et al*., 1995).

(*b*) *In-vitro studies*

(i) *Static magnetic fields*

Cell proliferation

Fibroblasts from fetal human lung were exposed to static magnetic fields of 0.2 T, 1.0 T and 1.5 T for 1 h per day on five consecutive days. Cell cycle analyses of synchronously and non-synchronously growing cells were conducted and population doublings (parameters used to describe cell growth) were calculated. The proliferation kinetics of the cells were analysed for 21 days to rule out mid-term effects. No statistically significant differences between exposed and sham-exposed cells were observed. The calculations of population doublings did not reveal any modulation of cell growth during

exposure. Proliferation kinetics did not provide evidence of any mid-term growth modulation effects of repeated exposure to magnetic fields (Wiskirchen *et al.*, 2000).

Fibroblasts from fetal human lung were exposed to a static 1.5-T magnetic field for 1 h three times a week for three weeks. Population doublings and cumulative population doublings were calculated weekly to detect treatment-related differences in overall cell growth. No significant differences between groups were found. Clonogenic activity, DNA synthesis, cell cycle and cell proliferation kinetics were not altered by exposure to the magnetic field (Wiskirchen *et al.*, 1999).

MCF-7 human breast cancer cells were exposed for different lengths of time (5–180 min) to the static magnetic field generated by a 0.2-T magnetic resonance tomograph. This treatment significantly decreased the incorporation of [^{3}H]thymidine into DNA in these cells (Pacini *et al.*, 1999a).

Gene expression

Exposure to a static magnetic field of 0.18–0.2 T for 1–6 days did not affect the growth of HeLaS3 cells. The effects of X-rays or heat treatment, which caused a transient delay in cell growth were not enhanced by subsequent exposure to the static magnetic field. Expression of the *c-fos* oncogene was measured in the HeLaS3 cells after exposure to the magnetic field for 2–24 h. No *c-fos* mRNA was detectable in unexposed cells, but it was expressed following incubation at a temperature of 45 °C for 10 and 15 min, and the expression was further enhanced by subsequent exposure of the cells to the magnetic field for 4 h (Hiraoka *et al.*, 1992).

Signal transduction

The effects of a static magnetic field generated by a 0.2-T magnetic resonance tomograph on cultured human neuronal cells (FNC-B4) were examined. Examination of the cells by scanning electron microscopy immediately after 15 min of exposure showed a significant change in cell morphology. At the same time, thymidine incorporation and inositol lipid signalling were significantly reduced. Sham-exposed control cells or non-neuronal cells (mouse leukaemia cells, human breast carcinoma cells) were unaltered. The release of endothelin-1 from FNC-B4 cells was much reduced after exposure to the magnetic field for only 5 min. However, no field-related alterations were found in 12 different DNA microsatellite sequences selected as indicators of genome instability (Pacini *et al.*, 1999b).

Apoptosis

Static magnetic fields generated by permanent magnetic discs showed an inhibitory effect on apoptotic cell death induced by various agents such as hydrogen peroxide, heat shock, ageing in culture and dexamethasone treatment in mitogen-stimulated human lymphocytes and certain human cell lines (U937, CEM and Burkitt

lymphoma cells). For U937 cells, the reduction in apoptosis was first evident at flux densities of 0.6 mT and increased in a dose-dependent fashion until 6 mT, at which a plateau was reached that extended to 66 mT. Similar results were seen for CEM cells, but there was no anti-apoptotic effect of exposure to static magnetic fields on human lymphocytes or Burkitt lymphoma cells. Studies to test the involvement of calcium ion influx suggested that the inhibitory effect of magnetic fields on apoptosis is mediated by an enhanced influx of calcium ions from the extracellular medium. Thus, this effect would be limited to cells in which calcium influx has an anti-apoptotic effect (Fanelli *et al.*, 1999).

Exposure of the human leukaemic cell line HL60 to a 50-Hz, 45-mT magnetic field for a minimum of 1 h induced an increase in the number of apoptotic cells, but this effect was not observed in lymphocytes from human peripheral blood (Hisamitsu *et al.*, 1997; Narita *et al.*, 1997). In mouse haematopoietic progenitor cells (FDCP-mix (A4)), no alteration in the frequency of apoptosis was detected after exposure to 50-Hz magnetic fields at 6 μT, 1 mT or 2 mT for various lengths of time up to seven days (Reipert *et al.*, 1997). Rat tendon fibroblasts and rat bone-marrow osteoprogenitor cells were exposed to static magnetic fields and 60- or 1000-Hz alternating fields at flux densities of up to 0.25 mT. Various combinations of field strengths and frequencies resulted in increased apoptosis and detachment of the cells from the substratum, or in failure to attach (Blumenthal *et al.*, 1997). An increased frequency of apoptotic cells was found in a transformed human squamous-cell carcinoma line (SCL-II), but not in a non-transformed human amniotic fluid cell line after exposure to a 50-Hz field with a flux density of about 1.0 mT (Simkó *et al.*, 1998b).

Ismael *et al.* (1998) examined spontaneous and dexamethasone-induced apoptosis in thymocytes and spleen cells from mice exposed to 60-Hz magnetic fields at 0.4–1 μT or static magnetic fields of 8–20 μT. The animals were exposed continuously (24 h per day) for 12 months. The relative weights of the thymus and the spleen did not differ between control and exposed groups. Cells were isolated from both these organs, incubated with or without dexamethasone (10^{-7} M) and examined for apoptosis. Spontaneous apoptosis was not different between groups. Statistically significant increases were observed in dexamethasone-induced apoptosis only in thymocytes from animals exposed to 60-Hz, 0.4–1.0-μT magnetic fields.

The results reviewed above may suggest an increase in apoptosis in some cell types under certain experimental conditions of exposure to electric or magnetic fields, but further studies would be useful.

(ii) *ELF electric and magnetic fields*

Cell proliferation

No significant change was observed in the proliferation characteristics of Chinese hamster ovary cells exposed to magnetic fields at either 220 μT or 5 mT (Livingston *et al.*, 1991; Miyakoshi *et al.*, 1996b). Oscillatory, time-dependent changes in cell proliferation, however, have been found in SV40-3T3 mouse fibroblasts after a single

1 h exposure to a 50-Hz, 2-mT magnetic field (Schimmelpfeng & Dertinger, 1997). In another study, a 30-min exposure to magnetic fields (50 Hz, 80 μT) caused an increase in the rate of proliferation of human epithelial amnion cells, but no effects were seen with other combinations of flux density and exposure duration (Kwee & Raskmark, 1995). SV40-transformed cells derived from a healthy donor and from an ataxia telangiectasia patient were exposed to an ELF magnetic field (50 Hz, 400 mT) for 2 h after pretreatment with 6 and 4 Gy X-rays, respectively. The magnetic field had no effect on the X-ray-induced reduction of survival of either cell line (Miyakoshi *et al*., 1994). When human myelogenous HL60 cells were exposed to an ELF magnetic field (45 mT) for 1 h, apoptotic cells were observed, but the same study found no apoptosis in human peripheral lymphocytes exposed under the same conditions (Narita *et al.*, 1997).

The effects of ELF pulsed fields on cell proliferation were studied in cultured human lymphocytes from 24 young and 24 old donors (mean ages, 24 and 86 years, respectively). The pulse duration of the fields was about 2 ms and the repetition rate was 50 Hz, yielding a duty cycle of 1/10. The intensity of the magnetic field was 2.5 mT, and its average time variation of the order of 1 T/s. The maximum induced electric field was estimated to be 0.02 mV/cm. The cultures were exposed for 24–66 h, and then incubated for a further 6 h to allow incorporation of [^{3}H]thymidine. The exposure to the pulsed fields had no effect on control lymphocytes but increased the phytohaemagglutinin-induced proliferation of the lymphocytes from the two donor groups. The effect was stronger in lymphocytes from old people. These cells normally show a reduced proliferative capability, but after exposure to the pulsed magnetic field, the incorporation of [^{3}H]thymidine was similar to that observed in lymphocytes from young subjects (Cossarizza *et al*., 1989b).

The effects of rapidly changing magnetic gradient fields were examined in fetal human lung fibroblasts exposed for 2–24 h to trapezoid-shaped waveforms of 500- and 75-Hz base frequency and an amplitude of 2 mT. Proliferation of the cells was monitored for three weeks after exposure. Cell cycle analysis was carried out until 24 h after cessation of exposure to detect alterations in cell division. No differences in proliferation or cell cycle distribution between exposed and unexposed cell cultures were observed (Rodegerdts *et al.*, 2000).

A study using human breast cancer MCF-7 cells (provided by D. Blask, Cooperstown, NY) reported the effects of exposure to ELF electric and magnetic fields on cell proliferation. When these cells were exposed to a sinusoidal electric and magnetic field (60 Hz, 1.2 μT) with concomitant melatonin treatment (10^{-9} M) the proliferation-inhibiting effect of this compound was reduced (Liburdy *et al.*, 1993). The same series of studies demonstrated that exposure to ELF sinusoidal, but not full-wave rectified, electric and magnetic fields reduced the ability of tamoxifen, an agent used clinically for the treatment of breast cancer, to inhibit cell proliferation (Harland & Liburdy, 1997; Harland *et al.*, 1999). These results, with respect to both melatonin and tamoxifen, have been independently replicated by Blackman *et al.* (2001) using the same cells, provided by the Liburdy laboratory. In a study with melatonin-

insensitive MCF-7 cells, obtained from the Japanese cell bank, no effect of exposure to fields of 60 Hz, 5 mT was observed on cell growth either in the presence or absence of melatonin (Tachiiri *et al.*, 1999). [The Working Group noted that some but not all MCF-7 cell lines are responsive to melatonin; responsiveness may depend on the presence of estrogen receptors in these cells.]

Exposure of the yeast *Saccharomyces cerevisiae* to a 50-Hz, 120-μT magnetic field delayed recovery from the growth inhibition induced by ultraviolet B (UVB) radiation. The progression of the cell cycle after UVB exposure was also modified by the magnetic field (Markkanen *et al.*, 2001).

The effects of exposure to pulsed electric and magnetic fields were studied in lymphocytes from the peripheral blood of 25 patients with Down syndrome, a disorder in which premature ageing is characterized by precocious immune system derangement, including age-related defective proliferative capability of lymphocytes. After exposure to the pulsed fields, a significant increase in phytohaemagglutinin-induced cell proliferation was observed in cells from children and young adults with Down syndrome, but this phenomenon was much more evident in lymphocytes from older Down syndrome patients (Cossarizza *et al.*, 1991).

In studies that have used incorporation of [^{3}H]thymidine into nuclear DNA as an indicator of cell proliferation, the effects of exposure to electric and magnetic fields on cell growth *in vitro* have been mixed. Human fibroblasts exposed to various frequencies (15–4000 Hz) of magnetic fields (2.3–560 μT) showed enhanced DNA synthesis (Liboff *et al.*, 1984). Exposures to 0.18–2.5-mT pulsed electromagnetic fields, at specific ranges of pulse width, pulse height and pulse repetition rate, also stimulated DNA synthesis in Chinese hamster V79 cells (Takahashi *et al.*, 1986). In contrast, exposure to ELF electric and magnetic fields (1–200 Hz, 230–650 μT) inhibited DNA synthesis in phytohaemagglutinin-induced human lymphocytes (Conti *et al.*, 1983; Mooney *et al.*, 1986), whereas no significant effect on DNA synthesis was seen in HL-19 normal human fibroblasts exposed for 30 h to 50-Hz magnetic fields over a wide range of flux densities (20 μT–20 mT) (Cridland *et al.*, 1996).

Gene expression

The transcription of the oncogene *c-myc* in human leukaemia HL60 cells was enhanced by a 20-min exposure to an ELF magnetic field (150–15 Hz: maximum expression at 45 Hz, 200 μT–2.3 mT) (Goodman & Shirley-Henderson, 1991; Goodman *et al*, 1994). It was also reported that chloramphenicol transferase expression was enhanced when a specific DNA region upstream of the *c-myc* gene was transfected into human HeLa cells as a chloramphenicol transferase construct, followed by a 20-min exposure to a 60-Hz, 8-μT magnetic field (Lin *et al.*, 1994). Other studies, however, have failed to reproduce the enhancement of *c-myc* expression by exposure to ELF electric and magnetic fields (Lacy-Hulbert *et al.*, 1995; Saffer & Thurston, 1995; Balcer-Kubiczek *et al.*, 1996; Miyakoshi *et al.*, 1996b). Exposure to an ELF magnetic field

(60 Hz, 1 mT, for 75 min) caused no change in transcription rate of *c-myc* or the β-actin gene in HL60 cells, but it enhanced transcription of 45S ribosomal-RNA (Greene *et al.*, 1993). [The Working Group noted that HL60 cells display a high endogenous level of *c-myc* expression.]

In human T-lymphoblastoid cells (CEM-CM3), the transcriptional activities of *c-fos*, *c-myc* and the protein kinase C gene, which are associated with signal transduction, were increased by exposure to a 60-Hz, 100-μT magnetic field although this effect was strongly dependent on the duration of exposure and the cell density during the assay (Phillips *et al.*, 1992).

A chloramphenicol transferase gene construct containing the upstream regulatory region of the *c-fos* gene (from base pair –700 to +42) was transfected into HeLa cells. The cells were then exposed to a 60-Hz, 6-μT magnetic field for up to 40 min. An approximately 1.2-fold increase in chloramphenicol transferase-protein expression was seen 60 min after a 20-min exposure (Rao & Henderson, 1996). [The Working Group noted that the chloramphenicol transferase activity appeared to be very low, suggesting that the response of the construct was poor under the conditions tested.]

Primary and immortalized rat tracheal epithelial cells exposed for 30 min to a 50-Hz, 100-μT magnetic field displayed an approximately 3-fold enhancement of *c-jun* protein expression. In the same study, however, *c-fos* expression was decreased to approximately 70% of control levels following a 5-h exposure to the magnetic field (Lagroye & Poncy, 1998). Exposure to 60-Hz magnetic fields at 5.7 or 570 μT for 10–40 min caused no change in *c-fos* mRNA expression in HL60 cells (Balcer-Kubiczek *et al.*, 1996).

Transcription of the gene encoding the heat shock protein hsp70 was increased by about 1.8-fold in HL60 cells exposed for 20 min to a 60-Hz, 8-μT magnetic field. Increased transcription of the heat shock gene *SSA1* in the yeast *Saccharomyces cerevisiae* was observed under the same conditions (Goodman *et al.*, 1994). By means of the chloramphenicol transferase assay, the increased expression of hsp70 in HL60 cells, induced by exposure to ELF magnetic fields (60 Hz, 8 μT), was shown to be caused by enhanced binding of the *c-myc* protein to sites within the heat shock protein promoter region (Lin *et al.*, 1998a,b). However, in C3H mouse mammary carcinoma-derived 34i cells, a 20-min exposure to magnetic fields (50 Hz, 1.5 and 3 mT) had no effect on the expression of hsp70 or hsp90 (Kang *et al.*, 1998). Likewise, 2–20 h of exposure to a 50-Hz, 50-mT magnetic field had no influence on the expression of hsp70 protein in HL60RG cells. In this study, however, hsp70 expression induced by mild heat treatment (40 °C or 42 °C) could be suppressed by simultaneous application of the magnetic field (Miyakoshi *et al.*, 2000b).

The exposure of Chinese hamster ovary cells to a 50-Hz, 400-mT magnetic field caused a transient increase (maximum approximately 6 h) in the expression of the gene encoding the neuron-derived orphan receptor 1 (NOR-1); exposure to a 5-mT field had no effect (Miyakoshi *et al.*, 1998b).

Signal transduction

The focus of several investigations on the effect of electric and magnetic fields on cellular signal transduction has been the role of calcium, since it is intimately involved in the regulation of many signal transduction pathways.

Mononuclear blood cells from healthy adult volunteers were stimulated with phytohaemagglutinin and exposed to a squared waveform field (3 Hz, 6 mT). The uptake of Ca^{2+} was lower than in cells treated with phytohaemagglutinin alone (Conti *et al.*, 1985). Conversely, exposure of rat thymocytes for 60 min to an induced 60-Hz electric field of 1.0 mV/cm produced an average 2.7-fold increase in concanavalin A-dependent Ca^{2+}-uptake compared to that in unexposed, isothermal control cells (Walleczek & Liburdy, 1990). Oscillatory increases in the concentration of intracellular calcium were induced in human Jurkat cells exposed to a 50-Hz, 0.1-mT magnetic field (Lindström *et al.*, 1993). In a further study, the same cells displayed oscillations in intracellular Ca^{2+} when exposed to magnetic fields with a wide frequency range (5–100 Hz), the strongest effect being seen at 50 Hz. At this frequency, the response showed a no-effect threshold at 0.04 mT, and a plateau at 0.15 mT (Lindström *et al.*, 1995a, 1996).

Oscillations of free intracellular calcium were seen in individual Jurkat cells in response to exposure to a 50-Hz, 0.15-mT magnetic field. In contrast, a CD45-deficient Jurkat cell line did not respond to stimulation by a magnetic field. The phosphatase activity of CD45 may regulate the activity of p56lck tyrosine kinase by removing an inhibitory phosphate. By using Jurkat cells that expressed a chimeric molecule, comprising the cytoplasmic phosphatase domain of CD45, the field-induced calcium response could be restored (Lindström *et al.*, 1995b).

Exposure to magnetic fields (50 Hz, 0.1 mT) also resulted in a significant increase in the concentration of inositol 1,4,5-trisphosphate in Jurkat cells. This effect was not inhibited by chelation of intracellular calcium ions, which implies that the oscillations in calcium concentration induced by the magnetic fields were not due to direct stimulation of the calcium-dependent phospholipase C-γ1, an enzyme involved in the formation of inositol 1,4,5-triphosphate (Korzh-Sleptsova *et al.*, 1995).

A later study reported that exposure to magnetic fields (60 Hz, 0.15 mT) had no effect on intracellular calcium signalling in Jurkat E6-1 cells (Lyle *et al.*, 1997).

Exposure of HL60 cells to an electric field (60 Hz, 10–100 V/m) for 1 h significantly decreased the activity of cytosolic protein kinase C. However, no concomitant rise in membrane-bound protein kinase C activity was observed, indicating that the electric field promotes down-regulation of cytosolic protein kinase C activity (Holian *et al.*, 1996).

Changes in signal transduction events as a result of exposure to magnetic fields have been described in a number of studies with human B-lineage lymphoid cells and chicken lymphoma B-cells (DT40). Other investigators, however, have failed to replicate these findings. Some of the studies are summarized below.

Exposure of human B lymphoid cells to a magnetic field (60 Hz, 0.1 mT) stimulated various tyrosine kinases, which resulted in tyrosine phosphorylation of many proteins and subsequent activation of phosphokinase C in a time-dependent manner. Analysis of various steps in the signal transduction pathway led the authors to conclude that the growth regulation of B lymphoid cells may be altered by the activation of a specific tyrosine kinase (Lyn) by the magnetic field (Uckun *et al.*, 1995).

Exposure of DT40 chicken lymphoma B cells to a vertical magnetic field (60 Hz, 0.1 mT) resulted in the activation of phospholipase C-γ2, leading to increased turnover of inositol phospholipids. This activation is mediated by Bruton's tyrosine kinase (BTK), which was shown to be the responsive target for interaction with the magnetic field (Kristupaitis *et al.*, 1998).

In an attempt to replicate the findings described above, Miller & Furniss (1998) examined the effects of magnetic fields on wildtype DT40 cells, on BTK-deficient DT40 cells and on BTK-deficient cells that had been reconstituted with the human *BTK* gene. The cells were all obtained from the Uckun laboratory. No effects were seen on production of inositol-1,4,5-trisphosphate, BTK-activation or tyrosine phosphorylation after exposure of these cells to 60-Hz, 0.1-mT magnetic fields. The authors suggest that the conflicting results may be due to some critical parameter in the exposure environment that is different between laboratories.

In a further study aimed at replication of previous findings, Woods *et al*. (2000) exposed human B lymphoid cells (obtained from Uckun's laboratory) and chicken lymphoma DT40 cells (obtained from Miller's laboratory, but originally from Uckun) to a 60-Hz, 0.1-mT magnetic field, with or without a parallel, static magnetic field of 0.046 mT. No significant changes were detected in tyrosine phosphorylation or in activation of Lyn and Syk tyrosine kinases in either cell line.

Exposure of β-galactosidase-transfected PC12-VG cells stimulated by forskolin to a 400-mT magnetic field for 4 h enhanced β-galactosidase expression. This enhanced expression was significantly inhibited by calcium entry blockers and almost completely suppressed by concomitant treatment with calphostin C, a protein kinase C inhibitor (Ohtsu *et al.*, 1995). The induction of expression of the neuron-derived orphan receptor (NOR-1) gene by exposure to a 50-Hz, 400-mT magnetic field was also inhibited by treatment with various Ca^{2+} influx inhibitors (Miyakoshi *et al.*, 1998b).

Ornithine decarboxylase activity is controlled by a signal transduction pathway associated with cell proliferation. In a study using human lymphoblastoid cells (CEM), mouse myeloma cells (P3) and rat hepatoma cells (Reuber H35), exposure to 60-Hz electric fields (10–1000 V/m) caused a transient, several-fold increase in the activity of ornithine decarboxylase (Byus *et al.*, 1987). A twofold increase in the activity of this enzyme was also seen in mouse L929 cells exposed to a 60-Hz magnetic field (1–100 μT) (Litovitz *et al.*, 1991). The same group also showed a dose–response relationship with a consistently elevated activity of ornithine decarboxylase at flux densities > 4 μT (Mullins *et al.*, 1999). However, two studies designed to replicate this result with L929 cells from the same or a different source, failed to find a significant

change in the activity of ornithine decarboxylase as a result of exposure to electric or magnetic fields (Azadniv *et al.*, 1995; Cress *et al.*, 1999).

Three mammalian tumour cell lines (human promyelocytic leukaemia HL60 cells, mouse ascites tumour ELD cells and mouse teratocarcinoma F9 cells) were used to determine the effects of exposure to magnetic fields on ornithine decarboxylase gene expression. All cell lines showed elevated levels of activity of the enzyme when exposed during culture to a 50-Hz, 30-μT vertical sinusoidal magnetic field for 24, 48 or 72 h. The increase ranged from about 20% in HL60 cells to up to five- to sixfold in ELD cells compared to the controls. The effect was stronger at later stages of growth, when the inherent activity of ornithine decarboxylase is lower (Mattsson & Rehnholm, 1993).

Two lymphoblastic leukaemia cell lines of human origin, Jurkat cells and CEM-CM3 cells, were exposed to horizontal or vertical magnetic fields (50 Hz, 0.10 mT). Exposure to the vertical magnetic field for 3 h or 3 days increased the activity of ornithine decarboxylase in the Jurkat cells by 77% and 47%, respectively. Only a small effect of exposure to the horizontal magnetic field was seen, perhaps due to the lower intensity of the induced electric field. However, the CEM-CM3 cells did not respond to either type of exposure (Valtersson *et al.*, 1997).

Growth factors and differentiation

The effects of pulsed electric and magnetic fields on mitogen-stimulated lymphocytes from aged human volunteers (mean age, 88 years) were studied by measuring the production of interleukin-2 and the expression of interleukin-2 receptor in these cells. The pulse duration of the magnetic field was about 2 ms, the repetition rate 50 Hz, the intensity 2.5 mT, and the average time variation was of the order of 1 T/s. The maximum induced electric field was estimated to be 0.02 mV/cm. Control cultures were maintained in the same incubator in a position where no electric or magnetic field was detectable. [The Working Group noted the close proximity of the control and the exposed samples.] Cultures were exposed for 18 h for evaluation of interleukin-2 receptor-positive cells and percentage of T-activated lymphocytes, and for 24 and 48 h for examining the production of interleukin-2. In exposed cultures that showed increased [^{3}H]thymidine incorporation compared with unexposed controls, the production of interleukin-2 was lower, but the percentages of interleukin-2 receptor-positive cells and of T-activated lymphocytes were increased (Cossarizza *et al.*, 1989c).

A study of the ability of nerve growth factor-stimulated PC-12 cells, derived from the rat adrenal medulla, to produce neurites under a variety of conditions of exposure to magnetic fields, was designed to establish those field parameters critical for production of biological effects. Twenty-three hours of exposure both to sub-optimal concentrations of nerve growth factor and to a flux density series of vertical, 45-Hz magnetic fields demonstrated reduced neurite outgrowth at flux densities between 5 and 10 μT, where the inhibition reached a plateau. The cell response at the periphery

of culture dishes of different diameter was identical to that at the centre of the dishes indicating that the induced electric current was not responsible for the effect (Blackman *et al*., 1993). The frequency response, which was tested from 15 Hz–70 Hz for each of six flux densities (3.5–9.0 μT), displayed frequency-specific profiles of inhibition of neurite outgrowth (Blackman *et al*., 1995). Trillo *et al*. (1996) showed that different specific flux densities of static and alternating magnetic fields (at 30 Hz, 0.79–2.05 μT alternating and 1.97 μT static; at 45 Hz, 0.29–4.11 μT alternating and 2.96 μT static) could produce a characteristic, but slightly different inhibition response, in which a narrow flux density region around the value that had produced maximal inhibition, displayed no inhibition. The effects observed using 45-Hz fields were not seen when the static field was reduced to 1.97 μT. Blackman *et al*. (1999) tested the frequency dependence of the findings of Trillo *et al*. (1996) using flux densities for maximum effects at 45 Hz and observed a maximal inhibition at 45 Hz with lesser inhibition at 42.5 and 47.5 Hz, and no inhibition at 40 and 50 Hz. Blackman *et al*. (1996) showed that the neurite outgrowth response changed from field-induced inhibition to enhancement when the static magnetic field was changed through a series of angles from parallel to perpendicular to the alternating magnetic field. In a study based on the work of Blackman and colleagues, McFarlane *et al.* (2000) observed a field-induced (50 Hz, 4–8 μT) inhibition (~ 22%) of neurite outgrowth in PC-12 cells cultured in 15% serum (weakly differentiating conditions) and enhancement (~ 17%) of the outgrowth in cells cultured in 4% serum (strongly differentiating conditions). No significant changes were observed at higher or lower flux densities.

A Friend erythroleukaemia cell line that can be chemically induced to differentiate was used to determine whether magnetic fields could alter cell proliferation and differentiation in a manner similar to that of a chemical tumour promoter. Exposure of this cell line to 60-Hz fields resulted in a dose-dependent inhibition of differentiation, with a maximal inhibition of 40% at 4 μT. Exposure at 2.5 μT caused a 20% inhibition while a 1-μT field was ineffective. At flux densities in the range of 0.1–1 mT, cell proliferation was stimulated up to 50% above that of sham-treated cells. The activity of telomerase, a marker of undifferentiated cells, decreased 100-fold when the cells were induced to differentiate under sham conditions, but only 10-fold when the cells were exposed to a 50-μT magnetic field. In summary, exposure to ELF electric and magnetic fields appears to partially block the differentiation of Friend erythroleukaemia cells, and this results in a larger population of cells remaining in the undifferentiated, proliferative state, which is similar to results obtained with chemical tumour promoters (Chen *et al*., 2000).

Intercellular communication

Ubeda *et al*. (1995) observed that the increased gap-junctional intercellular communication induced in C3H10T1/2 mouse embryo cells by physiological concentrations of melatonin, could be completely eliminated when the cells were exposed for 1 h to vertical, 50-Hz, sinusoidal magnetic fields at 1.6 mT.

Li *et al.* (1999) exposed Chinese hamster lung cells to the tumour promoter TPA alone or in combination with a 50-Hz magnetic field. Combined treatment with 5 ng/mL TPA for the last hour of a 24-h period of exposure to magnetic flux densities of 0.2, 0.4 or 0.8 mT, significantly inhibited gap-junctional intercellular communication compared with TPA treatment alone. The inhibition was dependent on the flux density.

Gap-junctional intercellular communication was also studied in clone 9 cells treated with 2.5 mM chloral hydrate for 24 h prior to exposure to a 45-Hz, 23.8-μT magnetic field, in parallel with a 36.6-μT static magnetic field for 40–45 min. There was no statistically significant effect of exposure to the magnetic field on gap-junctional intercellular communication (Griffin *et al.*, 2000).

Cell transformation

In a study using anchorage-independent growth as an index, mouse epidermal JB6 cells (clone 41) were exposed to magnetic fields (60 Hz, 1, 10 and 100 μT) for eight or 14 days, resulting in a 1.2–3.2-fold increase in colony-forming efficiency of transformants (West *et al.*, 1996). In contrast, in a co-culture of C3H10T1/2 mouse fibroblasts and mutant daughter 10e cells, intermittent exposure to an ELF magnetic field (60 Hz, 100 μT, 1 h, four times a day) for 28 days caused no increase in focus formation. In the same culture system, however, concomitant exposure to the magnetic field and treatment with TPA (10–100 ng/mL) caused a significant increase in focus formation (by an average of 150%) compared with that in cell cultures treated with TPA alone (Cain *et al.*, 1993).

There are reports suggesting that ELF electric and magnetic fields have no effect on cell transformation. In a soft-agar assay, 60-Hz magnetic fields of 0.01, 0.1, 1.0 or 1.1 mT flux density did not induce anchorage-independent growth of mouse epidermal JB6 cells, enhance TPA-induced transformation, increase the maximum number of transformed colonies or produce a shift in the dose–response curve (Saffer *et al.*, 1997). Similarly, in another study, continuous exposure to a magnetic field of 60 Hz, 200 μT for 24 h showed no effect in two transformation systems (Syrian hamster embryo cells and CH310T1/2 clone 8) with or without post-treatment with TPA (Balcer-Kubiczek *et al.*, 1996).

Cultures of primary Syrian hamster dermal cells were continuously exposed to power-line frequency magnetic fields of 10, 100 and 1000 μT for 60 h, with or without prior exposure to an immortalizing dose (1.5 Gy) or a non-immortalizing dose (0.5 Gy) of ionizing radiation. Exposure to the magnetic field alone did not immortalize these cells at a detectable frequency (1×10^{-7} or higher) or enhance the frequency of immortalization induced by ionizing radiation (Gamble *et al*, 1999). The lack of cell-transforming activity of pulsed electric and electric and magnetic fields had previously been shown in a BALB/3T3 cell transformation assay (Jacobson-Kram *et al.*, 1997).

CH310T1/2 clone 8 cells were exposed for 24 h to strong magnetic fields (5–400 mT, 60 Hz) to investigate a change in transformation frequency as analysed by

focus formation. No significant increase in transformation frequency was seen after exposure to the magnetic fields alone, but exposure to 3 Gy X-rays followed by exposure to the magnetic fields for 24 h decreased the transformation frequency in comparison with exposure to X-rays alone. In addition, long-term exposure for six weeks at 60 Hz, 5 mT significantly suppressed both spontaneous and X-ray-induced transformation (Miyakoshi *et al.*, 2000c).

4.5 Mechanistic considerations

Limited data are available on the effects of static fields alone. Therefore, the following considerations of a possible mechanism will address primarily ELF electric and magnetic fields.

It is widely agreed that certain alterations in the genetic structure of the cell are causally related to cancer. There is little experimental or theoretical evidence that mutations could be directly caused by ELF magnetic fields. The results of most genetic toxicology studies of ELF magnetic fields have been negative. However, a single laboratory has reported that exposure of human cells to extremely high ELF flux densities ($\geq$ 400 mT), which far exceeds the field intensities encountered in residential or occupational environments, induces sister chromatid exchange, chromatid-type aberrations and mutation in the *HPRT* gene.

It is also relevant to ask whether ELF electric and magnetic fields have effects similar to those of known 'non-genotoxic' carcinogens, 'tumour promoters' or 'co-carcinogens', i.e. agents that seem to enhance cancer by a mechanism other than that of direct DNA damage.

There is little evidence that ELF electric or magnetic fields can cause malignant transformation of cells in culture. There have been relatively few studies of the effects of ELF electric and magnetic fields on DNA repair or genomic stability in mammalian cells, and the results are inconclusive. There is some evidence for an effect of magnetic fields on cellular kinetics: few studies using in-vitro systems have shown enhancement of apoptosis. The results of studies on cell proliferation using a variety of exposure conditions and cell types have varied from inhibition to enhancement. The cell-proliferation response to physical and chemical factors has also been reported to be altered by exposure to ELF magnetic fields. The available experimental evidence suggests that ELF electric or magnetic fields are not cytotoxic.

The effects of ELF electric and magnetic fields on signal transduction have been reported to include changes in intracellular calcium levels and protein phosphorylation, but a number of studies have reported negative findings. These results cannot be used to identify plausible cancer-related pathways.

Several research groups have reported changes in gene expression resulting from exposure to ELF magnetic fields. However, other studies have failed to replicate many of these results.

In relation to both the genotoxic and non-genotoxic cellular and molecular end-points that have been studied, many of the data concern changes evoked following a combined exposure: that is, experiments involving (electric or) magnetic fields together with other agents. There is only weak evidence that ELF magnetic fields potentiate the effects of chemical agents, or ionizing or ultraviolet radiation.

The risk for cancer can also be enhanced through systemic effects in humans or animals. For example, it has been suggested that the hormone melatonin may suppress mammary cancer through hormonal mechanisms; anticarcinogenic effects through free-radical scavenging have also been proposed. Several human and animal studies have investigated possible suppressing effects of ELF magnetic fields on melatonin, but the results are equivocal. Although most experimental studies of the possible immunotoxicity of exposure to magnetic fields have yielded negative results, effects on T-cell proliferation capacity in animals have been reported. However, the effects are inconsistent.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Static electric and magnetic fields arise from both natural and man-made sources, whereas electric and magnetic fields in the extremely low-frequency (ELF) range (3–3000 Hz) are mostly associated with man-made sources. These are numerous and include electric power systems, electric and electronic appliances and industrial devices. Environmental levels of ELF fields are very low. Exposure levels for the general population are typically 5–50 V/m for electric fields and 0.01–0.2 μT for magnetic fields. Considerably higher exposure occurs for shorter durations and in some occupational settings.

It should be noted that the earth's magnetic field (25–65 μT, from equator to poles) is a static field to which everyone is exposed.

Measurements of electric and magnetic fields are used to characterize sources and levels of exposure to humans. The capabilities of instruments to measure such fields have advanced in recent years, particularly for magnetic fields. In addition to simple, easy-to-use hand-held survey instruments, there are now portable personal exposure meters capable of recording and describing the statistical, threshold, frequency and waveform characteristics of magnetic field exposure. The limiting factor in exposure assessment is not instrumentation but the lack of a consensus as to what exposure characteristics should be measured that are biologically relevant.

Computational methods are available to calculate fields and their parameters for instrument calibration, laboratory exposure systems and certain categories of indoor and outdoor sources. The difficulties in the use of computation methods to characterize exposure to magnetic fields include the lack of complete knowledge as to the magnitude, direction and location of all relevant current flows on conductors. Such difficulties pose special challenges to the use of calculations of ELF magnetic fields to estimate historical exposure from power lines. Where computational methods are used to calculate human exposure in epidemiological studies, it is desirable to understand the overall uncertainty in the calculated values.

In order to understand the effects of electric and magnetic fields on animals and humans, their electrical properties have to be considered. Static magnetic fields, which are not attenuated by the organism, can exert forces on moving charges, orient magnetic structures and affect the energy levels of some molecules. Static and ELF electric fields are greatly attenuated inside the body.

Exposure to ELF electric and magnetic fields results in induction of electric fields and associated currents in tissues. The magnitudes and spatial patterns of these fields depend on whether the external field is electric or magnetic, its characteristics (e.g. frequency, magnitude, orientation and waveform) and the size, shape and electrical properties of the exposed body. This is a basic physical mechanism for interaction of ELF magnetic fields with tissues. The induced electric field increases with the frequency of the external field and the size of the object. A well-established effect of induced fields above a threshold level is the stimulation of excitable cells. Typical residential exposure results in very small induced electric fields, while some occupational exposure and exposure directly under very high-voltage power lines may result in electric fields of the order of 1 mV/m in some tissues. Non-perceptible contact currents under some conditions are calculated to produce electric fields exceeding 1 mV/m in the bone marrow of a child. Residential levels of ELF electric and magnetic fields produce much lower fields in tissues.

Beyond this well-established interaction mechanism, a number of hypotheses have been advanced: radical pair mechanisms, ion charge-to-mass resonance mechanisms, stochastic resonance, action on biogenic magnetite, etc. Theoretical and experimental evidence for the relevance of these mechanisms is being sought actively.

There are well established in-vivo and in-vitro exposure systems that can provide electric fields of up to the order of 150 kV/m and ELF magnetic fields up to 2 mT. Magnetostatic fields up to 5.0 T can be produced in the laboratory.

5.2 Human carcinogenicity data

Effects in children

Since the first report suggesting an association between residential ELF electric and magnetic fields and childhood leukaemia was published in 1979, dozens of increasingly sophisticated studies have examined this association. In addition, there have been numerous comprehensive reviews, meta-analyses, and two recent pooled analyses. In one pooled analysis based on nine well conducted studies, no excess risk was seen for exposure to ELF magnetic fields below 0.4 μT and a twofold excess risk was seen for exposure above 0.4 μT. The other pooled analysis included 15 studies based on less restrictive inclusion criteria and used 0.3 μT as the highest cut-point. A relative risk of 1.7 for exposure above 0.3 μT was reported. The two studies are closely consistent. In contrast to these results for ELF magnetic fields, evidence that electric fields are associated with childhood leukaemia is inadequate for evaluation.

No consistent relationship has been seen in studies of childhood brain tumours or cancers at other sites and residential ELF electric and magnetic fields. However, these studies have generally been smaller and of lower quality.

The association between childhood leukaemia and high levels of magnetic fields is unlikely to be due to chance, but it may be affected by bias. In particular, selection bias

may account for part of the association. Case-control studies which relied on in-home measurements are especially vulnerable to this bias, because of the low response rates in many studies. Studies conducted in the Nordic countries which relied on historical calculated magnetic fields are not subject to selection bias, but suffer from very low numbers of exposed subjects. There have been dramatic improvements in the assessment of exposure to electric and magnetic fields over time, yet all of the studies are subject to misclassification. Non-differential misclassification of exposure (similar degrees of misclassification in cases and controls) is likely to result in bias towards the null. Bias due to unknown confounding factors is very unlikely to explain the entire observed effect. However, some bias due to confounding is quite possible, which could operate in either direction. It cannot be excluded that a combination of selection bias, some degree of confounding and chance could explain the results. If the observed relationship were causal, the exposure-associated risk could also be greater than what is reported.

Numerous studies of the relationship between electrical appliance use and various childhood cancers have been published. In general, these studies provide no discernable pattern of increased risks associated with increased duration and frequency of use of appliances. Since many of the studies collected information from interviews that took place many years after the time period of etiological interest, recall bias is likely to be a major problem.

Studies on parental occupational exposure to ELF electric and magnetic fields in the preconceptional period or during gestation are methodologically weak and the results are not consistent.

Effects in adults

Residential exposure

While a number of studies are available, reliable data on adult cancer and residential exposure to ELF electric and magnetic fields, including the use of appliances, are sparse and methodologically limited. None of the studies reported so far has included long-term or personal measurements. Although there have been a considerable number of reports, a consistent association between residential exposure and adult leukaemia and brain cancer has not been established.

For breast cancer and other cancers, the existing data are not adequate to test for an association with exposure to electric or magnetic fields.

Occupational exposure

Studies conducted in the 1980s and early 1990s pointed to a possible increased risk of leukaemia, brain tumours and male breast cancer in jobs with presumed exposure to ELF electric and magnetic fields above average levels. The interpretation of these studies was difficult mainly due to methodological limitations and lack of

appropriate exposure measurements. Also, a bias towards publication of positive findings could not be excluded.

Several large studies conducted in the 1990s of both leukaemia and brain cancer made use of improved methods for individual assessment of occupational exposure to magnetic fields, and to potential occupational confounders, mainly through the combined use of systematic workplace measurements, individual job history descriptions, and the development of associated job–exposure matrices. However, because the exposure within occupational groups is highly variable, job–exposure matrices do not eliminate all uncertainties regarding the workers' exposure levels. Some of these studies reported increased cancer risk for intermediate or high magnetic field exposure categories. There was no consistent finding across studies of an exposure–response relationship and no consistency in the association with specific sub-types of leukaemia or brain tumour. Evidence for cancers at other sites was not adequate for evaluation.

Although the assessment of exposure to electric fields is difficult, these fields have been measured occasionally in populations of workers using individual exposure meters. Across the studies, no consistent association of electric field strengths with any particular malignancy was noted.

5.3 Animal carcinogenicity data

Four long-term bioassays have been published in which the potential oncogenicity in experimental animals of exposure to ELF magnetic fields was evaluated in over 40 different tissues using standard chronic toxicity testing designs. Three of the studies were conducted in rats (two in both sexes including one with restricted histopathological evaluation, and one in females only) and one in mice (males and females). Three of the four studies (two rat studies and one mouse study) provide no evidence that exposure to ELF magnetic fields causes cancer in any target organ. The fourth found an increased incidence of thyroid C-cell tumours (adenomas plus carcinomas) in male rats exposed to ELF magnetic fields at two intermediate flux densities, which did not demonstrate a dose–response relationship, and a marginal increase at the highest flux density. In the lowest-exposure group, thyroid C-cell carcinomas significantly exceeded control response and were above the historical control range. Thyroid C-cell carcinomas were not seen in male mice, female mice or female rats exposed chronically to ELF magnetic fields in these oncogenicity bioassays.

A long-term oncogenicity bioassay of more limited design that was conducted to identify possible effects of exposure to ELF magnetic fields on the induction of leukaemia and lymphoma or of brain cancer in mice generated negative results.

Two multistage carcinogenesis studies combining exposure to *N*-methyl-*N*-nitrosourea with exposure to static or 50-Hz magnetic fields were performed in the same laboratory using an uncharacterized outbred rat strain. The first study demonstrated an increase in mammary tumour incidence with exposure to the fields regardless of

exposure to *N*-methyl-*N*-nitrosourea. The second study showed no effect at similar exposure levels.

Eleven multistage carcinogenesis studies combining exposure to 7,12-dimethylbenz[*a*]anthracene with exposure to 50- or 60-Hz magnetic fields were performed in three different laboratories. One laboratory performed six 13-week studies and one 27-week study aimed at addressing exposure–response relationships for different magnitudes of exposure to magnetic fields. These studies reported significant increases in mammary tumour incidence at higher exposure levels. A pooled analysis of exposure–response from these studies yielded an average slope significantly different from zero. A second laboratory conducted three studies (two of which were considered inadequate to assess tumour incidence) to replicate these findings at the highest field strengths, but saw no enhancement of mammary tumorigenesis by exposure to ELF magnetic fields in one study, in which the sham control incidence was low enough to detect an increase. In the two other studies, high incidences of mammary tumours in sham controls limited comparisons to possible increases in tumour multiplicity; none were found. The third laboratory studied the impact of intermittent exposure to magnetic fields and saw no changes in tumour incidence or tumour multiplicity in either of two experiments.

Eight studies were performed in five different laboratories on promotion and/or co-promotion of skin tumorigenesis by 50- or 60-Hz magnetic fields using conventional mouse strains. The results of these studies were generally negative. However, a suggestion of accelerated progression to malignancy was observed in one study and a change in tumour multiplicity was observed in another. There was no consistent pattern of response in these studies, which were of effectively equivalent design. One study using a transgenic mouse model demonstrated an acceleration of skin tumorigenesis by ELF magnetic fields.

Three studies have been performed using the enzyme-altered liver foci model in rats or mice to determine tumour promoting and co-promoting effects of 50-Hz magnetic fields (0.5–500 μT). No enhancement of liver foci by magnetic field exposure was reported in two studies in rats. In the third study which used ionizing radiation with and without exposure to magnetic fields, the incidence of basophilic liver foci was significantly increased in exposed mice. This finding was not associated with a significant increase in liver cancer incidence.

Multistage studies have been carried out in both mice (conventional and transgenic strains) and rats to evaluate the effects of ELF magnetic fields on the development of leukaemia and lymphoma. In no study did exposure to ELF magnetic fields cause an increased incidence of leukaemia or lymphoma.

One study was performed to identify possible promoting effects of ELF magnetic field exposure on the induction of neurogenic tumours. The results of this study showed no enhancement of neurogenic tumour induction.

5.4 Other relevant data

Reproductive effects in humans and animals

Taken as a whole, the results of human studies do not establish an association of adverse reproductive outcomes with exposure to ELF electric and magnetic fields. Such adverse outcomes have been reported in a few studies, particularly at higher field intensities and in people exposed for longer durations. With exposures from video display terminals, a greater number of studies have been performed and these generally found no adverse reproductive effects.

Experiments with many different mammalian and non-mammalian experimental models consistently indicate lack of adverse effects on reproduction and development from exposure to strong static magnetic (0.25–1.0 T) and ELF electric (up to 150 kV/m) fields. Static magnetic fields with high spatial gradients and those mixed with alternating fields have been reported to affect embryonic development in frogs and mice, although the number of studies is small.

Prenatal exposure to ELF magnetic fields generally does not result in adverse effects on reproduction and development in mammals. When effects are observed, they usually consist of minor developmental anomalies. Non-mammalian classes of animals (fish, frogs, birds) show inconsistent effects of ELF electric and magnetic fields on development (including increased malformations).

Other effects in humans

Due to the small number of immunological and haematological studies in humans and very small sample sizes within the reported studies, no health-related conclusions can be drawn from the data on immunological and haematological effects after exposure to ELF electric and magnetic fields.

In humans, the principal element of neuroendocrine response to exposure to ELF electric and magnetic fields that has been investigated is the circadian production and release of melatonin. No effect on melatonin was seen following night-time exposure of human volunteers to 50 or 60-Hz magnetic fields under controlled laboratory conditions. In contrast, a small reduction in melatonin concentration has been observed in occupational and residential environments, but it is difficult to distinguish between effects of the magnetic field and those of other environmental factors.

Apart from established perceptual responses in humans to ELF electric fields at levels of tens of kilovolts per meter and the occurrence of magnetophosphenes (faint, flickering visual sensations) in response to exposure to relatively strong ELF magnetic fields (> 10 mT at 20 Hz), few behavioural effects of exposure to ELF electric and magnetic fields have been observed. Changes in electroencephalograms, cognition, mood, sleep electrophysiology and cardiac response tend to be few, subtle and transitory when they do occur during exposure. The evidence from epidemiological studies of residential and occupational exposure to ELF electric and magnetic fields in

relation to the incidence of neurodegenerative disease, depression and suicide and cardiovascular disease is generally weak and inconsistent.

Other effects in animals

Studies to evaluate immune function and host resistance in animals have given negative effects for exposure to ELF electric and magnetic fields. In-vitro exposure of immune system cells generally did not cause changes in proliferation capacity.

Apart from occasional changes in some haematological parameters in one rat study, no consistent effects on blood formation were seen in experimental animals or their offspring exposed to either static magnetic fields or to 50- or 60-Hz electric and/or magnetic fields.

Most animal studies of endocrine function concern the pineal gland and melatonin, because of concerns related to cancer. Fewer studies have been carried out on the effects of exposure to ELF electric and magnetic fields on the pituitary hormones or those of other endocrine glands.

Some, but not all, studies of the effects of 50- or 60-Hz electric and magnetic fields in rodents show a reduction in pineal and/or serum melatonin concentrations. Differences in response have been reported for linearly polarized compared with circularly polarized magnetic fields. No convincing effect on melatonin concentrations has been seen in non-human primates chronically exposed to 50- or 60-Hz electric or magnetic fields.

With the possible exception of short-term stress (duration of minutes) following the onset of exposure to ELF electric fields at levels significantly above perception thresholds, no consistent effects have been seen in the stress-related hormones of the pituitary–adrenal axis in a variety of mammalian species.

Animals can perceive ELF electric fields (threshold 3–35 kV/m) and respond with activity changes or aversion. Such responses are generally not observed with magnetic fields.

Although exposure to magnetic fields has been reported to influence spatial learning and memory in rodents, it appears that no long-term behavioural deficits occur due to exposure to static or ELF electric and magnetic fields.

Genetic and related effects

A few studies on genetic effects have examined chromosomal aberrations and micronuclei in lymphocytes from workers exposed to ELF electric and magnetic fields. In these studies, confounding by genotoxic agents (tobacco, solvents) and comparability between the exposed and control groups are of concern. Thus, the studies reporting an increased frequency of chromosomal aberrations and micronuclei are difficult to interpret.

Many studies have been conducted to investigate the effects of ELF magnetic fields on various genetic end-points. Although increased DNA strand breaks have been reported in brain cells of exposed rodents, the results are inconclusive; most of the studies show no effects in mammalian cells exposed to magnetic fields alone at levels below 50 mT. However, extremely strong ELF magnetic fields have caused adverse genetic effects in some studies. In addition, several groups have reported that ELF magnetic fields enhance the effects of known DNA- and chromosome-damaging agents such as ionizing radiation.

The few animal studies on cancer-related non-genetic effects are inconclusive. Results on the effects on in-vitro cell proliferation and malignant transformation are inconsistent, but some studies suggest that ELF magnetic fields affect cell proliferation and modify cellular responses to other factors such as melatonin. An increase in apoptosis following exposure of various cell lines to ELF electric and magnetic fields has been reported in several studies with different exposure conditions. Numerous studies have investigated effects of ELF magnetic fields on cellular end-points associated with signal transduction, but the results are not consistent.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukaemia.

There is *inadequate evidence* in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to all other cancers.

There is *inadequate evidence* in humans for the carcinogenicity of static electric or magnetic fields and extremely low-frequency electric fields.

There is *inadequate evidence* in experimental animals for the carcinogenicity of extremely low-frequency magnetic fields.

No data relevant to the carcinogenicity of static electric or magnetic fields and extremely low-frequency electric fields in experimental animals were available.

Overall evaluation

Extremely low-frequency magnetic fields are *possibly carcinogenic to humans (Group 2B).*

Static electric and magnetic fields and extremely low-frequency electric fields are *not classifiable as to their carcinogenicity to humans (Group 3).*

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LIST OF ABBREVIATIONS

AC: alternating current
ALL: acute lymphoblastic leukaemia
AMEX: average magnetic exposure (a personal exposure meter)
AML: acute myeloid leukaemia
ANLL: acute non-lymphocytic leukaemia
bw: body weight
CI: confidence interval
CLL: chronic lymphocytic leukaemia
CML: chronic myeloid leukaemia
DC: direct current
DMBA: 7,12-dimethylbenz[*a*]anthracene
EEG: electroencephalogram
ELF: extremely low frequency (the frequency range from 3–3000 Hz)
EMDEX: electric and magnetic field digital exposure system (a personal exposure meter)
ENU: *N*-ethyl-*N*-nitrosourea
Fe_3O_4: magnetite
γGT: γ-glutamyltranspeptidase
GST-P: glutathione-*S*-transferase, placental form
HRV: heart rate variability
ICD: International Classification of Diseases
IEC: International Electrotechnical Commission
IEEE: Institute of Electrical and Electronics Engineers, USA
JEM: job–exposure matrix
MDS: myelodysplastic syndrome
MNU: *N*-methyl-*N*-nitrosourea
MRI: magnetic resonance imaging
NDEA: *N*-nitrosodiethylamine
NRPB: National Radiological Protection Board
ODC: ornithine decarboxylase
OHCC: ordinary high current configuration

OLCC: ordinary low current configuration
OR: odds ratio
PEM: personal exposure meter
PEMF: pulsed electromagnetic fields
PIR: proportionate incidence ratio
PMR: proportionate mortality ratio
PRR: proportionate registration ratio
rms: root-mean-square (see Glossary)
SIR: standardized incidence ratio
SMR: standardized mortality ratio
TPA: 12-*O*-tetradecanoylphorbol 13-acetate
TWA: time-weighted average (see Glossary)
UG: underground (buried cables)
VDT: video (visual) display terminal
VDU: video display unit
VHCC: very high current configuration
VLCC: very low current configuration
VLF: very low frequency

GLOSSARY

Atmospherics: the electromagnetic processes associated with lightning discharges (also called ‘sferics’)

Busbars: electrical connections between the transformer and other parts of an electricity substation.

Characteristics: detailed physical properties of electric or magnetic fields, such as the magnitude, frequency spectrum, polarization, etc.

Counterion polarization: the physical phenomenon responsible for the dispersion at low frequencies.

Dosimeter: an instrument that can be worn on the body of a person for measuring exposure over time.

Electric field: a vector field **E** measured in volts per metre.

Electromagnetic fields: the combination of electric and magnetic fields in the environment. This term is often confused with ‘electromagnetic radiation’ and can therefore be misleading when used with extremely low frequencies for which the radiation is barely detectable. For this reason the term ‘electric and magnetic fields’ is used throughout this Monograph.

Electrostatic fields: static fields produced by fixed potential differences.

Exposure: the amount of a chemical or physical agent in the environment that a person comes into contact with over a period of time.

Exposure assessment: the evaluation of a person’s exposure by measurements, modelling, information about sources or other means.

Exposure metric: a single number that summarizes exposure to an electric and/or magnetic field. The metric is usually determined by a combination of the instrument’s signal processing and the data analysis performed after the measurement.

Frequency response: the output of an instrument as a function of frequency relative to the magnitude of the input signal. The specification of the frequency response of an instrument includes the type of filter and its bandwidth.

Gap junction: an aqueous pore or channel through which neighbouring cell membranes are connected.

Geomagnetic field: magnetic field originating from the earth (including the atmosphere). Predominantly a static magnetic field, but includes some oscillating components and transients.

Harmonic (frequency): frequencies that are integral multiples of the power frequency or some other reference frequency.

High-voltage power lines: usually taken to mean power lines operating at 100 kV or 132 kV (also referred to as transmission lines).

Intermittent fields: fields with a root-mean-square vector magnitude that changes rapidly. In contrast to transients, intermittent fields may reach high levels for longer times and are generally in the ELF frequency range.

Magnetic field: In studies at extremely low frequency, this term is generally used for the magnetic flux density (B field).

Magnetic field strength: a vector field **H** with units of ampere per metre.

Magnetic flux density: a vector field **B** with units of tesla.

Magnetostatic fields: static fields established by permanent magnets and by steady currents.

Phosphenes: weak visual sensations that occur in response to magnetic fields (threshold, 20 Hz, 8 mT) or by direct electrostimulation. The effect is believed to result from the interaction of the induced current with electrically excitable cells in the retina.

Power frequency: the frequency at which AC electricity is generated. For electric utilities, the power frequency is 60 Hz in North America, Brazil and parts of Japan, and 50 Hz in much of the rest of the world.

Right-of-way: corridor of defined width within which the power line runs.

Root-mean-square (rms): the most versatile mathematical function for averaging the magnitude of time-varying electric and magnetic fields.

Spot measurement: an instantaneous measurement at a designated location.

Static field: a field vector that does not vary with time. In most environments, electric and magnetic fields change with time, but their frequency spectrum has a component at 0 Hz. This 'quasi-static' component of the field can be measured by averaging the oscillating signal over the sample time.

Time-weighted average (TWA): a weighted average of exposure measurements taken over a period of time with the weighting factor equal to the time interval between measurements. When the measurements are made with a monitor with a fixed sampling rate, the TWA is equal to the arithmetic mean of the measurements.

Transients: brief bursts of high-frequency fields, usually resulting from mechanical switching of AC electricity.

Transmission lines: *see* high-voltage power lines.

Transposed phasing: arrangement in which the wires or bundles of wire — phases — in the circuit on one side of the tower have the opposite order to those on the other side. This arrangement results in fields that decrease more rapidly with distance from the lines than other configurations.

Voxels: cubic cells with sides of 1–10 mm used to represent animal and human tissues in dosimetry models.

Waveform: a single component of the field measured as a function of time by an instrument with a response time much faster than the field's frequency of oscillation. The term also refers to the shape of the wave as displayed on a graph or oscilloscope trace.

Wire coding: a non-intrusive method for classifying homes on the basis of their distance from visible electrical installations and the characteristics of these installations.

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IARC Scientific Publications, IARC Handbooks and IARC CancerBases are also available from Oxford University Press, Walton Street, Oxford, UK OX2 6DP (Fax: +44 1865 267782).

IARC Monographs are also available in an electronic edition,
both on-line by internet and on CD-ROM, from GMA Industries, Inc.,
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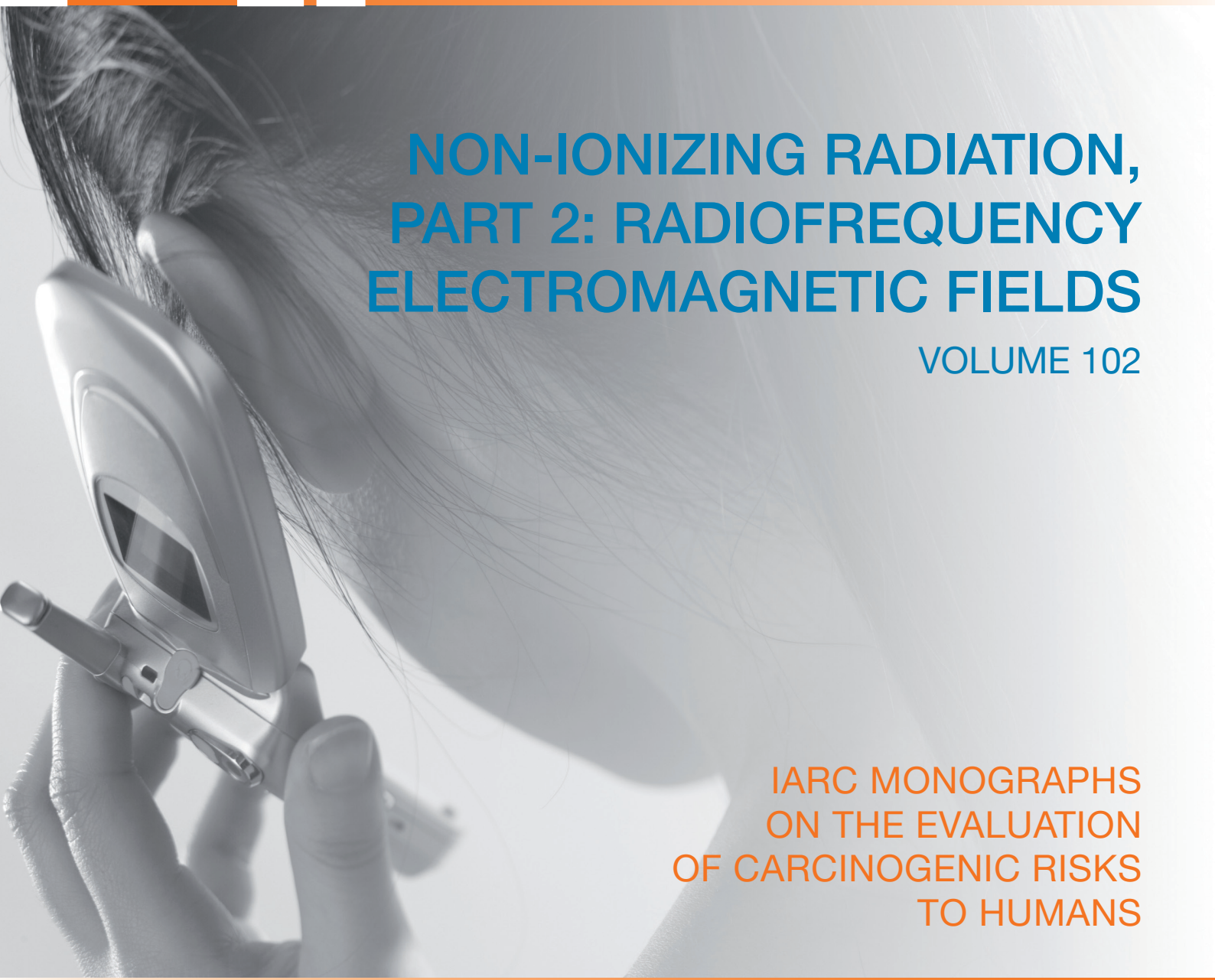
(Fax: +01 410 267 6602; internet: https//www.gmai.com/Order_Form.htm)

IARC MONOGRAPHS



NON-IONIZING RADIATION, PART 2: RADIOFREQUENCY ELECTROMAGNETIC FIELDS

VOLUME 102

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS

NON-IONIZING RADIATION, PART 2: RADIOFREQUENCY ELECTROMAGNETIC FIELDS

VOLUME 102

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 24-31 May 2011

LYON, FRANCE - 2013

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the Health, Safety and Hygiene at Work Unit of the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities, and since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the U.S. National Cancer Institute, the U.S. National Institute of Environmental Health Sciences, the U.S. Department of Health and Human Services, or the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities.

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NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 4 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US$1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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[5] Malcolm Sim owns stock (less than €5000) in Telstra, an Australian telecommunication-service provider.
[6] Luc Verschaeve's research institute received a small research grant (less than €5000, ceased in March 2011) from the GSM Operators Forum on environmental effects of mobile-phone base stations.
[7] Anders Ahlbom served (until May 2011) on the Board of Directors of Gunnar Ahlbom AB, a consulting firm in the domains of European Union affairs, especially within telecommunications.
[8] Niels Kuster is Director and Board member of the non-profit IT'IS Foundation that performs exposure assessments for industry and governments, and also President of the Board and shareholder of Near-Field Technology AG, a holding controlling two companies, SPEAG and ZMT, that are active in the development of near-field measurement instruments, simulation software and medical-test equipment.

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[9] Each Observer agreed to respect the Guidelines for Observers at IARC Monographs meetings. Observers did not serve as meeting chair or subgroup chair, draft any part of a Monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.

[10] Joe Elder is self-employed as a radiofrequency bioeffects consultant. He was employed by Motorola (until 2009) and his wife holds stock in Motorola. His participation as an Observer in this IARC Monographs meeting is sponsored by the Mobile Manufacturers Forum representing manufacturers of mobile and wireless communication devices and the network infrastructure that supports them.

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[12] Mays Swicord worked as a consultant for Motorola (until 2008). His participation as an Observer in this IARC Monographs meeting is sponsored by CTIA – The Wireless Association.

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate

or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data
Studies of cancer in humans
Studies of cancer in experimental animals
Mechanistic and other relevant data
Summary
Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are

obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population

to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for

confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they

allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in

an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo

transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls,

particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and

the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:** A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:** The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:** There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In

addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:** Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics,

physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental

animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity*

in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

This one-hundred-and-second volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of radiofrequency electromagnetic fields. This is the second volume on non-ionizing radiation, after Volume 80 (Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields; IARC, 2002), and the fourth and last in a series on physical agents, after Volume 75 (Ionizing Radiation, Part 1: X- and Gamma-radiation, and Neutrons; IARC, 2000) and Volume 78 (Ionizing Radiation, Part 2: Some Internally Deposited Radionuclides; IARC, 2001). Solar radiation and ultraviolet radiation were evaluated in Volume 55 (IARC, 1992). The types of radiation evaluated as human carcinogens (Group 1) were revisited in Volume 100D (IARC, 2012). A summary of the findings in the present volume has appeared in *The Lancet Oncology* (Baan *et al.*, 2011)

The topic of this *Monograph* is the evaluation of the carcinogenicity of radiation in the radiofrequency (RF) range (30 kHz to 300 GHz) of the electromagnetic spectrum. This type of radiation is emitted by devices used in wireless telecommunication, including mobile phones, and by many other sources in occupational and general environmental settings. Exposures are ubiquitous in more developed countries and rapidly increasing in developing countries, in particular with respect to the use of mobile phones. There is rising concern as to whether exposure to RF radiation emitted by a mobile phone affects human health and, specifically, whether mobile-phone use increases the risk of cancer of the brain. The general public, manufacturers, regulatory authorities and public health agencies are seeking evidence on the safety of mobile-phone use. Consequently, there has been intense interest in the development and outcome of this *IARC Monograph*. This interest reflects the high prevalence of exposure (which increasingly extends to children), the vast scope of the telecommunications industry, the findings of some epidemiological studies that suggest an increased risk of cancer, and a high level of media coverage of the topic of mobile phones and cancer.

Although the preparation of this *Monograph* had been scheduled so as to include the results of the large international case–control study INTERPHONE on mobile-phone use (conducted in 2000–2004; published in 2010), it should be emphasized that the evaluations in this volume address the general question of whether RF radiation causes cancer in humans or in experimental animals: it does not specifically or exclusively consider mobile phones, but rather the type of radiation emitted by mobile phones and various other sources. Furthermore, this *Monograph* is focused on the potential for an increased risk of cancer among those exposed to RF radiation, but does not provide a quantitative assessment of any cancer risk, nor does it discuss or evaluate any other potential health effects of RF radiation.

The Working Group recognized that mobile-phone technology has transformed the world, making wireless communication rapidly available, especially in less developed countries, with important

benefits to society. With this, an increasingly large population will be exposed, and for longer and longer periods of time. Undoubtedly, questions will continue to arise about the health risks of mobile-phone use and possibly other emerging sources of exposure to RF radiation. This *Monograph* is a comprehensive review of the currently published evidence that also identifies gaps in the available information. These gaps should be resolved with further research if ongoing concerns about the health risks of mobile-phone use are to be addressed with greater certainty.

The Working Group agreed to consider three categories of human exposure to RF radiation: (a) environmental sources such as mobile-phone base stations, broadcast antennae, smart meters, and medical applications; (b) occupational sources such as high-frequency dielectric and induction heaters, and high-power pulsed radars; and (c) the use of personal devices such as mobile phones, cordless phones, Bluetooth devices, and amateur radios.

The general population receives the highest exposure from transmitters close to the body, including hand-held devices such as mobile phones, which deposit most of the RF energy in the brain. Holding a mobile phone to the ear to make a voice call can result in high specific rates of absorption (SAR) of RF energy in the brain, depending on the design and position of the phone and its antenna in relation to the head, the anatomy of the head, and the quality of the connection with the base-station antenna: the better the connection, which is ensured by a dense network of base stations, the lower the energy output from the phone. In children using mobile phones, the average deposition of RF energy may be two times higher in the brain and up to ten times higher in the bone marrow of the skull than in adult users. The use of hands-free kits lowers exposure of the brain to less than 10% of the exposure from use at the ear, but it may increase exposure to other parts of the body.

Typical environmental exposures to the brain from mobile-phone base stations on rooftops and from television and radio stations are several orders of magnitude lower than those from GSM (Global System for Mobile communications) handsets. The average exposure from DECT (Digital Enhanced Cordless Telecommunications) phones is around five times lower than that measured for GSM phones, and third-generation (3G) phones emit, on average, about 100 times less RF energy than second-generation GSM phones, when signals are strong. Similarly, the average output power of Bluetooth wireless hands-free kits is estimated to be around 100 times lower than that of mobile phones. In occupational settings, exposure to high-power sources may involve higher cumulative deposition of RF energy in the body than with exposure to mobile phones, but the energy deposited locally in the brain is generally less.

Epidemiological evidence of an association between RF radiation and cancer comes from time-trend, cohort, and case–control studies. The populations in these studies were exposed to RF radiation in occupational settings, from sources in the general environment, and from use of wireless (mobile and cordless) phones. Two sets of data from case–control studies were considered by the Working Group as the principal and most informative basis for their evaluation of the human evidence, i.e. the INTERPHONE study and the Swedish case–control studies; both sets of data focused on brain tumours among mobile-phone users.

The Working Group recognized not only the rapid increase worldwide in the use of wireless communication systems – both in number of users and in duration of use – but also the considerable technological developments in this area, with the introduction of third- and fourth-generation (3G and 4G) devices during the past decade. It is of interest to note that the key epidemiological studies mentioned above were conducted in the late 1990s and the early 2000s. In the INTERPHONE study, all participating countries in Europe had GSM networks. It is worth mentioning that the 3G and 4G

mobile phones commercially available today – equipped with adaptive power control – emit considerably less RF energy than the GSM phones used more than a decade ago.

Experimental evidence from cancer bioassays was evaluated by the Working Group after reviewing more than 40 studies that assessed the incidence of tumours in rodents exposed to RF radiation at various frequencies, some of which simulated emissions from mobile phones. In the evaluation of studies of cancer in experimental animals, exposure assessment deserves critical consideration. In this regard, the conduct of cancer bioassays with RF radiation presents challenges that are not ordinarily encountered in studies with chemical or other physical agents. For example, the radiation frequency is an important determinant of the specific absorption rate (SAR). The whole-body SAR provides little information about spatial or organ-specific energy deposition, as it strongly depends on field polarization and animal posture. Furthermore, long-term exposure to RF radiation at a fixed frequency and power density will result in substantial changes in SAR over time as an animal gains body weight. Even if the power is adjusted for body weight changes, the spatial distribution can vary. Full dosimetric analyses of all these variables are only available in a few studies. Furthermore, SARs to which animals can be exposed without the induction of systemic toxicity are generally limited by the induction of thermal effects; increases in body temperature may induce biological responses that are not seen at the (generally much lower) levels of RF radiation to which humans may be exposed. In a substantial number of studies, exposure was at SAR values below the maximum tolerated dose (MTD); nonetheless, these studies were considered to provide useful data, and were included in the evaluation.

Several cancer bioassays with RF radiation were conducted with exposure systems in which animals were restrained (usually in tubes) or non-restrained (in cages) during exposure. In this *Monograph*, study designs involving animal restraint were identified as such. Exposures involving animal restraint are generally limited to periods of no more than 4 hours per day. They have the advantage of optimal exposure uniformity and maximal local delivery of RF-radiation energy to the head or other selected body parts. Exposure of animals in cages – whole-body exposure – can be for up to 24 hours per day. The design of some bioassays with restrained animals included both sham-exposed and cage-control animals; because of the possibly confounding effects of restraint stress, the Working Group compared tumour responses in the exposed groups only to the responses in sham-exposed controls. Lack of a sham-exposed control group was considered a serious flaw in the study design.

The Working Group reviewed a large number of studies with end-points relevant to mechanisms of carcinogenesis, including genotoxicity, effects on immune function, gene and protein expression, cell signalling, oxidative stress, and apoptosis. Studies on the possible effects of RF radiation on the blood–brain barrier, and on a variety of effects in the brain itself were also considered. The Working Group found several studies inadequately controlled for the thermal effects of RF radiation, but also noted well conducted studies showing aneuploidy, spindle disturbances, altered microtubule structures or induction of DNA damage. While RF radiation has insufficient energy to directly produce genetic damage, other changes such as induction of oxidative stress and production of reactive oxygen species may explain these results. Indeed, several studies *in vitro* evaluated the possible role of RF radiation in altering levels of intracellular oxidants or activities of antioxidant enzymes. While the overall evidence was inconclusive, the Working Group expressed concern about the results from several of these studies.

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1. EXPOSURE DATA

1.1 Introduction

This chapter explains the physical principles and terminology relating to sources, exposures and dosimetry for human exposures to radiofrequency electromagnetic fields (RF-EMF). It also identifies critical aspects for consideration in the interpretation of biological and epidemiological studies.

1.1.1 Electromagnetic radiation

Radiation is the process through which energy travels (or "propagates") in the form of waves or particles through space or some other medium. The term "electromagnetic radiation" specifically refers to the wave-like mode of transport in which energy is carried by electric (E) and magnetic (H) fields that vary in planes perpendicular to each other and to the direction of energy propagation.

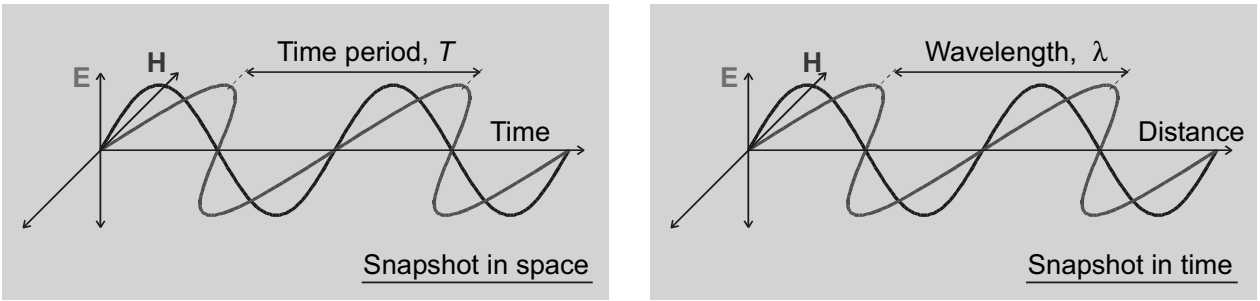
The variations in electric and magnetic field strength depend only on the source of the waves, and most man-made sources of electromagnetic radiation produce waves with field strengths that vary sinusoidally with time, as shown in Fig. 1.1. The number of cycles per second is known as the frequency (f) and is quantified in the unit hertz (Hz). The waves travel at the speed of light (c) in free space and in air, but more slowly in dielectric media, including body tissues. The wavelength (λ) is the distance between successive peaks in a wave (Fig. 1.1) and is related to the frequency according to $\lambda = c/f$ (ICNIRP, 2009a).

The fundamental equations of electromagnetism, Maxwell's equations, imply that a time-varying electric field generates a time-varying magnetic field and vice versa. These varying fields are thus described as "interdependent" and together they form a propagating electromagnetic wave. The ratio of the strength of the electric-field component to that of the magnetic-field component is constant in an electromagnetic wave and is known as the characteristic impedance of the medium (η) through which the wave propagates. The characteristic impedance of free space and air is equal to 377 ohm (ICNIRP, 2009a).

It should be noted that the perfect sinusoidal case shown in Fig. 1.1, in which a wave has a sharply defined frequency, is somewhat ideal; man-made waves are usually characterized by noise-like changes in frequency over time that result in the energy they carry being spread over a range of frequencies. Waves from some sources may show purely random variation over time and no evident sinusoidal character. Some field waveforms, particularly with industrial sources, can have a distorted shape while remaining periodic, and this corresponds to the presence of harmonic components at multiples of the fundamental frequency (ICNIRP, 2009a).

The quantities and units used to characterize electromagnetic radiation are listed in Table 1.1.

Fig. 1.1 A sinusoidally varying electromagnetic wave viewed in time at a point in space (a) and in space at a point in time (b)



(a) **(b)**

E, electric field; H, magnetic field.
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1.1.2 The electromagnetic spectrum

The frequency of electromagnetic radiation determines the way in which it interacts with matter; a variety of different terms are used to refer to radiation with different physical properties. The electromagnetic spectrum, describing the range of all possible frequencies of electromagnetic radiation, is shown in Fig. 1.2.

For the purposes of this *Monograph*, radiofrequency (RF) electromagnetic radiation will be taken as extending from 30 kHz to 300 GHz, which corresponds to free-space wavelengths in the range of 10 km to 1 mm. Electromagnetic fields (EMF) in the RF range can be used readily for communication purposes as radio waves. As shown in Fig. 1.2, the International Telecommunications Union (ITU) has developed a categorization for radio waves according to their frequency decade: very low frequency (VLF); voice frequency (VF); low frequency (LF); medium frequency (MF); high frequency (HF); very high frequency (VHF); ultra-high frequency (UHF); super-high frequency (SHF); and extremely high frequency (EHF) (ITU, 2008).

Radio waves with frequencies in the range 300 MHz to 300 GHz can be referred to as microwaves, although this does not imply any sudden change in physical properties at 300 MHz. The photon energy would be about 1 μeV (microelectronvolt) at 300 MHz.

Above the frequencies used by radio waves are the infrared, visible ultraviolet (UV), X-ray and gamma-ray portions of the spectrum. At RF and up to around the UV region, it is conventional to refer to the radiation wavelength, rather than frequency. Photon energy is generally referred to in the X-ray and gamma-ray regions, and also to some extent in the UV range, because the particle-like properties of the EMFs become more obvious in these spectral regions.

Below the RF portion of the spectrum lie EMFs that are used for applications other than radiocommunication. The interdependence of the electric- and magnetic-field components also becomes less strong and they tend to be considered entirely separately at the frequency (50 Hz) associated with distribution of electricity (IARC, 2002).

1.1.3 Exposures to EMF

RF fields within the 30 kHz to 300 GHz region of the spectrum considered in this *Monograph* arise from a variety of sources, which are considered in Section 1.2. The strongest fields to which people are exposed arise from the intentional use of the physical properties of fields, such as

Table 1.1 Quantities and units used in the radiofrequency band

Quantity	Symbol	Unit	Symbol
Conductivity	σ	siemens per metre	S/m
Current	I	ampere	A
Current density	J	ampere per square metre	A/m^2
Electric-field strength	E	volt per metre	V/m
Frequency	*f*	hertz	Hz
Impedance	Z or η	ohm	Ω
Magnetic-field strength	H	ampere per metre	A/m
Permittivity	ε	farad per metre	F/m
Power density	S or Pd	watt per square metre	W/m^2
Propagation constant	K	per metre	m^{-1}
Specific absorption	SA	joule per kilogram	J/kg
Specific absorption rate	SAR	watt per kilogram	W/kg
Wavelength	λ	metre	m

Adapted from ICNIRP (2009a)

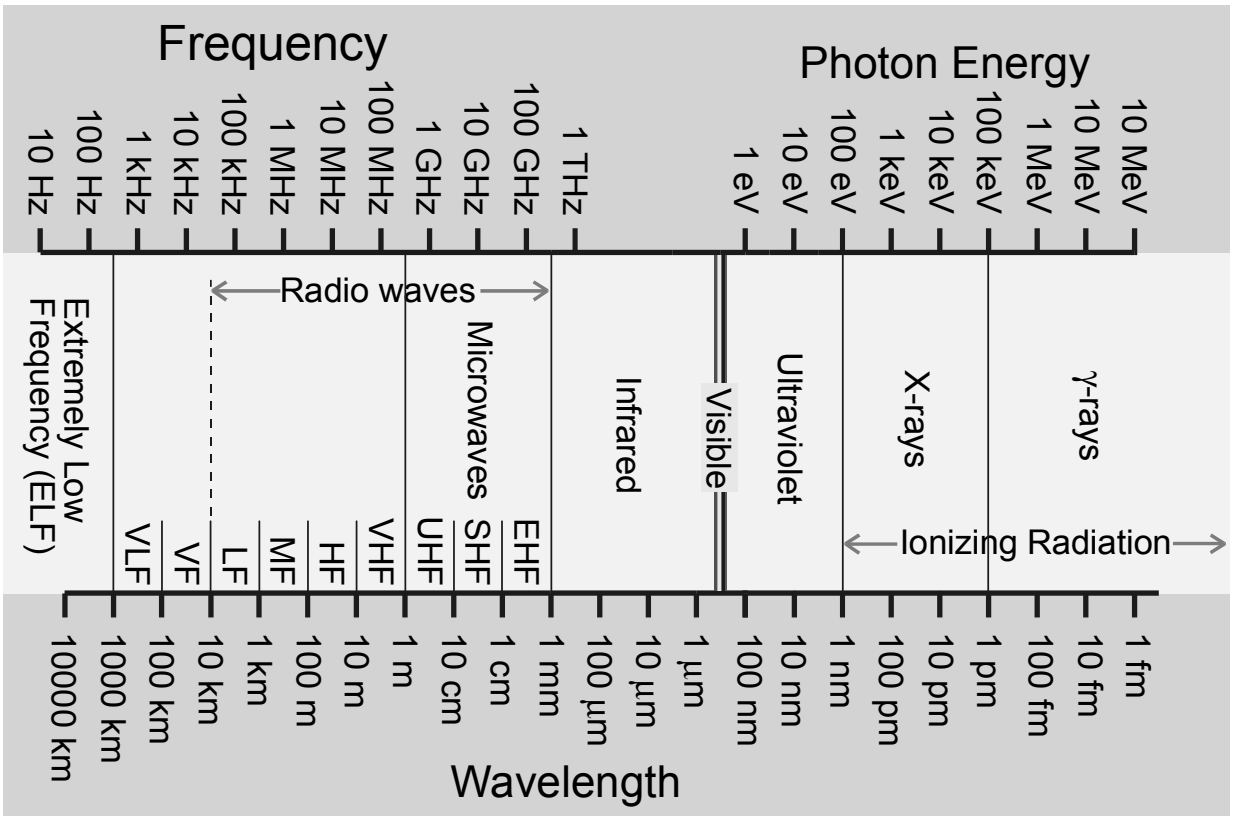
induction heating (including the industrial heating of materials and cooking hobs), remote detection of objects and devices (anti-theft devices, radar, radiofrequency identification [RFID]), telecommunications (radio, television, mobile phones, wireless networks), medical diagnostics and therapy (magnetic resonance imaging [MRI], hyperthermia), and many more. There are also unintentionally generated fields, such as those associated with the electrical ballasts used for fluorescent lighting, electronic circuits, processors and motors.

When considering human exposures it is important to recognize that, in addition to the EMFs associated with energy being radiated away from a source, there are electric and magnetic fields associated with energy stored in the vicinity of the source, and this energy is not propagating. The reactive fields associated with this stored energy are stronger than the radiated fields within the region known as the reactive near field, which extends to a distance of about a wavelength from the source. The wave impedance in the reactive near field may be higher than the impedance of free space if a source is capacitive in nature and lower if a source is inductive in nature (AGNIR, 2003).

Beyond the near field region lies the far field, where the RF fields have the characteristics of radiation, i.e. with planar wave fronts and E and H components that are perpendicular to each other and to the direction of propagation. The power density of the radiation, P_d, describes the energy flux per unit area in the plane of the fields expressed as watts per square metre (W/m^2) and decreases with distance squared (the inverse square law). Power density can be determined from the field strengths (see Glossary) (AGNIR, 2003).

Sources that are large relative to the wavelength of the RF fields they produce, e.g. dish antennae, also have a region known as the radiating near field that exists in between the reactive near field and the far field. In this region the wave impedance is equal to 377 ohm, but the wave fronts do not have planar characteristics: there is an oscillatory variation in power density with distance and the angular distribution of the radiation also changes with distance. Since the radiating near field is taken to extend to a distance of $2D^2/\lambda$ (where D is the largest dimension of the antenna) from the source, it is therefore necessary to be located beyond both this distance and

Fig. 1.2 The electromagnetic spectrum



The figure shows frequency increasing from left to right expressed in hertz (Hz) and in kHz (kilo-), MHz (mega-), GHz (giga-) and THz (tera-) (denoting multipliers of 10^3, 10^6, 10^9 and 10^{12}). Electromagnetic fields in the radiofrequency (RF) range can be used for communication purposes as radio waves. Mobile phones operate in the low-microwave range, around 1 GHz. The terms VLF, VF, LF, MF, HF, VHF, UHF, SHF, EHF denote very low frequency, voice frequency, low frequency, medium frequency, high frequency, very high frequency, ultra-high frequency, super-high frequency, and extremely high frequency, respectively.
Beyond the frequencies used by radio waves follow the infrared, visible, ultraviolet, X-ray and gamma-ray portions of the spectrum. Above radiofrequencies and up to around the ultraviolet region, it is conventional to refer to the wavelength (expressed in metres and its multipliers) of the radiation, rather than frequency. Below the radiofrequency portion of the spectrum lie electromagnetic fields that are used for applications other than radiocommunications. Photon energy is expressed in electronvolts (eV and its multipliers).
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about a wavelength from a source to be in the far-field region (AGNIR, 2003).

The incident EMFs (external fields when the body is not present) interact or couple with the human body and induce EMFs and currents within the body tissues. A different interaction mechanism exists for the electric- and magnetic-field components, as discussed in detail in Section 1.3. In general, both quantities must be determined to fully characterize human exposure, unless the exposure is to pure radiating fields. The coupling depends on the size of the wavelength relative to the dimensions of the human body and, therefore, dosimetric interactions are often considered in three different frequency ranges: 30 kHz to 10 MHz (body larger than the wavelength), 10 MHz to 10 GHz (body dimensions comparable to the wavelength), and 10 GHz to 300 GHz (body dimensions much larger than the wavelength).

1.2 Sources of exposure

This section describes natural and man-made sources of RF fields to which people are exposed during their everyday lives at home, work and elsewhere in the environment. Fields from natural and man-made sources differ in their spectral and time-domain characteristics and this complicates comparisons of their relative strengths. The fields produced by natural sources have a much broader frequency spectrum than those produced by man-made sources and it is necessary to define a bandwidth of interest for comparison. In a bandwidth of 1 MHz, man-made fields will typically appear to be orders of magnitude stronger than natural ones, whereas if the entire bandwidth of 300 GHz of interest to this *Monograph* is chosen, natural fields may appear to be stronger than man-made ones at typical environmental levels (ICNIRP, 2009a).

When considering sources, it is helpful to clearly delineate the concepts of emissions, exposures and dose:

Emissions from a source are characterized by the radiated power, including its spectral and time-domain distributions: the polarization and the angular distribution (pattern) of the radiation. For sources that are large relative to their distance from a location where a person is exposed, it also becomes necessary to consider the spatial distribution of the emitted radiation over the entire structure of the source to fully describe it as an emitter.

Exposure describes the EMFs from the source at a location where a person may be present in terms of the strength and direction of the electric and magnetic fields. If these vary over the volume occupied by a person (non-uniform exposure), possibly because the source is close to them, or has strongly directional characteristics, it becomes necessary to quantify the RF fields over the space occupied by the person. The exposure depends not only on the source emissions and the geometrical relationship to the source (distance, angular direction), but also on the effect of the environment on the radiated fields. This can involve processes such as reflection, shielding, and diffraction, all of which can modify the fields substantially.

Dose is concerned with quantities of effects inside the body tissues that are induced by the exposure fields. These include the electric- or magnetic-field strength in the body tissues and the specific energy absorption rate (SAR) (see Section 1.3.2, and Glossary). The strength of the electric fields within the body tissues is generally much smaller than that of the exposure fields outside the body, and depends on the electrical parameters of the tissues (Beiser, 1995).

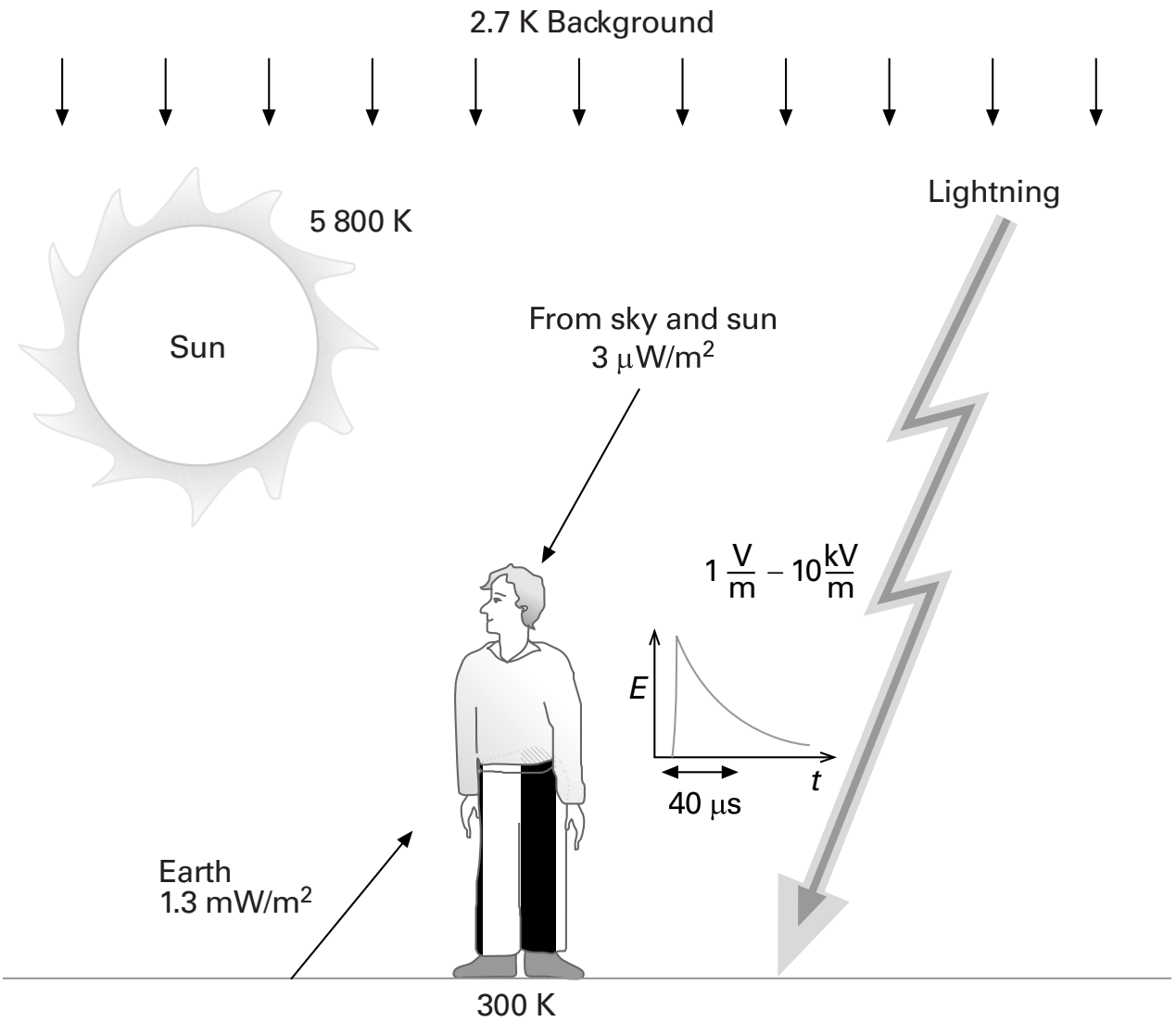
In most situations, the concept of emissions leading to exposure and then dose is helpful, but there are situations in which the presence of an exposed individual and the dose received affect the emissions from a source. This means that the intermediate concept of exposure cannot be isolated meaningfully, and dose has to be assessed directly from the source emissions either through computational modelling or via measurement of fields inside the body tissues. When the way in which a source radiates is strongly affected by the presence of an exposed person, the source and the exposed person are described as "mutually coupled"; a classic example of this is when a mobile phone is used next to the body.

1.2.1 Natural fields

The natural electromagnetic environment originates from the Earth (terrestrial sources) and from space (extraterrestrial sources) (Fig. 1.3). Compared with man-made fields, natural fields are extremely small at RFs (ICNIRP, 2009a).

The energy of natural fields tends to be spread over a very wide range of frequencies. Many natural sources emit RF radiation and optical radiation according to Planck's law of "black-body radiation" (see Fig. 1.4; Beiser, 1995).

Fig. 1.3 Terrestrial and extraterrestrial sources of radiofrequency radiation



E, electric field strength; K, Kelvin; kV, kilovolt; m, metre; μs, microsecond; t, time; V, volt; W/m^2, watt per square metre.
The solar radiation spectrum is similar to that of a black body with a temperature of about 5800 °K. The sun emits radiation across most of the electromagnetic spectrum, i.e. X-rays, ultraviolet radiation, visible light, infrared radiation, and radio waves. The total amount of energy received by the Earth at ground level from the sun at the zenith is approximately 1000 W/m^2, which is composed of approximately 53% infrared, 44% visible light, 3% ultraviolet, and a tiny fraction of radio waves (3 μW/m^2).
From ICNIRP (2009a) http://www.icnirp.de

Fig. 1.4 Equations used in calculating energy and emitted power of black-body radiators

$$S(f,T) = \frac{2hf^2}{c^2}\frac{1}{e^{\frac{hf}{kT}}-1}$$

(a) Planck's Law of "black body radiation"

S(f,T) is the power radiated per unit area of emitting surface in the normal direction per unit solid angle per unit frequency by a black body at temperature T.

h is the Planck constant, equal to 6.626×10^{-34} Js.

c is the speed of light in a vacuum, equal to 2.998×10^{8} m/s.

k is the Boltzmann constant, equal to 1.381×10^{-23} J/K.

f is the frequency of the electromagnetic radiation in hertz (Hz).

T is the temperature of the body in Kelvin (K).

$$J^* = \sigma T^4$$

(b) Stefan-Boltzmann Law

J* , the black-body irradiance or emissive power, is directly proportional to the fourth power of the black-body thermodynamic temperature T (also called absolute temperature).

σ, the constant of proportionality, called Stefan-Bolzmann constant.

The total power emitted per unit surface area of a black-body radiator can be evaluated by integrating Planck's law over all angles in a half-space (2π steradians) and over all frequencies. This yields the Stefan-Boltzmann law (see Fig. 1.4), which describes how the power emitted by a black-body radiator increases with the fourth power of the absolute temperature (Beiser, 1995).

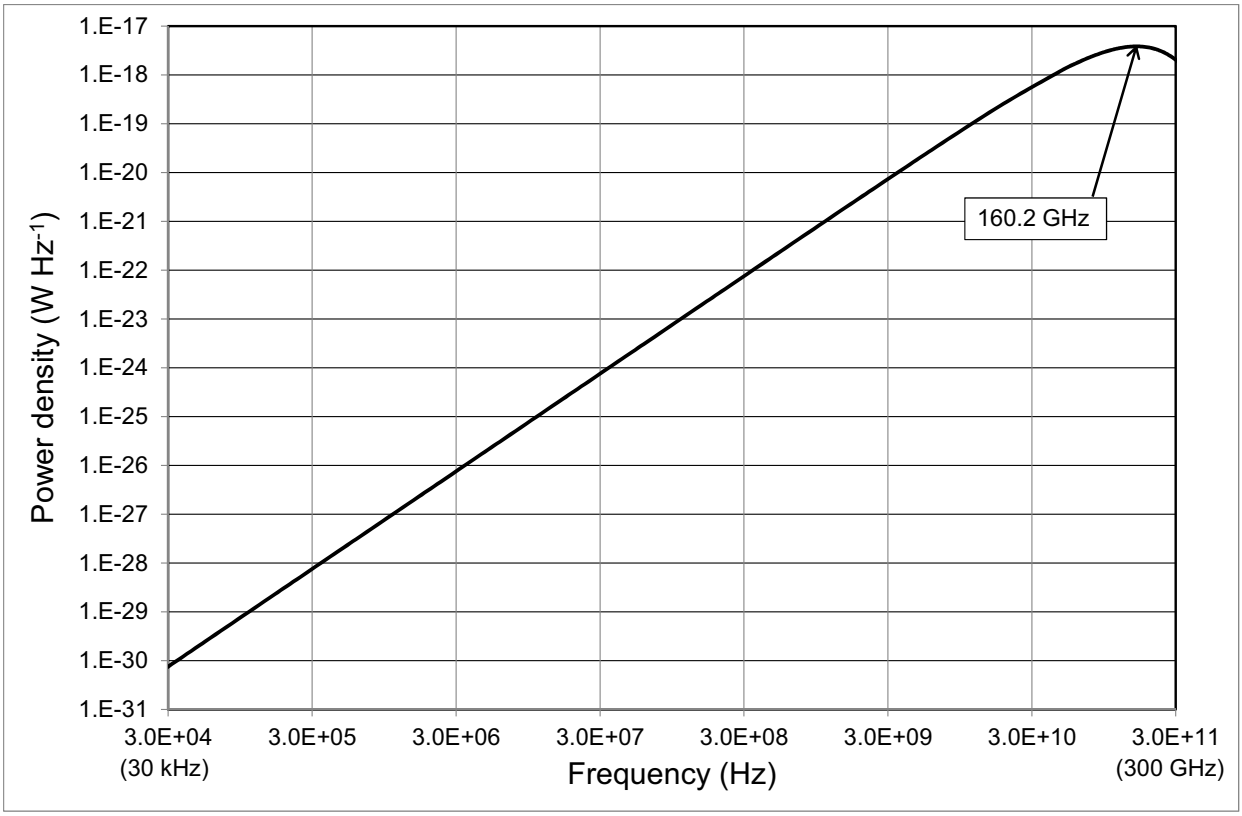
(a) Extraterrestrial sources

Extraterrestrial sources include electrical discharges in the Earth's atmosphere, and solar and cosmic radiation. Heat remaining from the "big bang" at the formation of the universe is evident as the cosmic microwave background (CMB), which presents as black-body radiation from all directions towards the Earth. The observed peak in the CMB spectrum is at a frequency of 160.2 GHz, which according to Planck's law (see Fig. 1.4) implies a temperature of 2.725 K (Fixsen, 2009). Fig 1.5 shows the results of evaluating Planck's law over the frequency range 30 kHz to 300 GHz. The total power density in this frequency range represents 80% of the total power density across all frequencies. Applying this factor to the results from Stefan-Boltzmann's law at 2.725 K gives the power density at the surface of the Earth as 2.5 μW/m^2.

The sun is also a black-body radiator and its spectrum shows a peak at 3.4×10^{14} Hz, a wavelength of 880 nm, commensurate with a surface temperature of 5778 K (NASA, 2011). Based on Planck's law, most of the sun's radiation is in the infrared region of the spectrum. Only a small proportion is in the frequency range 30 kHz to 300 GHz; this fraction represents about 5 μW/m^2 of the total power density of 1366 W/m^2 incident on the Earth. This value is similar to that from the CMB, which contributes power from all directions, but the RF power from the sun is predominantly incident from the direction of the sun, and hence much reduced at night (ICNIRP, 2009a).

The atmosphere of the Earth has a marked effect on RF fields arriving from space. The ionosphere, which extends from about 60 km to 600 km above the Earth's surface, contains layers of charged particles and reflects RF fields at frequencies of up to about 30 MHz. Above a few tens of gigahertz, atmospheric water vapour and oxygen have an attenuating effect on RF fields, due to absorption. These effects mean that the RF power density incident at the Earth's surface

Fig. 1.5 Power density spectrum of the cosmic microwave background in the radiofrequency range (30 kHz to 300 GHz)



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from the sun and the CMB will be somewhat less than the 5 μW/m^2 values given for each above. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) gives the total power density arising from the sky and the sun as 3 μW/m^2 at the surface of the Earth (see Fig. 1.3; ICNIRP, 2009a).

(b) Terrestrial sources

The Earth itself is a black-body radiator with a typical surface temperature of about 300 K (see Fig. 1.3). Most emissions from Earth are in the infrared part of the spectrum and only 0.0006% of the emitted power is in the RF region, which amounts to a few milliwatts per square metre from the Earth's surface. This is about a thousand times larger than the RF power density arising from the sky and the sun (ICNIRP, 2009a).

People also produce black-body radiation from their body surfaces (skin). Assuming a surface temperature of 37 °C, i.e. 310 K, the power density for a person would be 2.5 mW/m^2 in the RF range. With a typical skin area of 1.8 m^2, the total radiated power from a person is about 4.5 mW.

As mentioned above, the ionosphere effectively shields the Earth from extraterrestrially arising RF fields at frequencies below 30 MHz. However, lightning is an effective terrestrial source of RF fields below 30 MHz. The fields are generated impulsively as a result of the time-varying voltages and currents associated with lightning, and the waveguide formed between the surface of the Earth and the ionosphere enables the RF fields generated to propagate over large distances around the Earth.

On average, lightning strikes the Earth 40 times per second, or 10 times per square kilometre per year. Maps of annual flash rates based on observations by National Aeronautics and Space Administration (NASA) satellites can be consulted on the National Oceanic and Atmospheric Administration (NOAA) web site (NOAA, 2011). The EMFs from lighting are impulsive and vary depending on the nature of each stroke and also according to the distance at which they are measured. A typical pulse-amplitude of 4 V/m at 200 km corresponds to a peak power density of 42 mW/m^2, and a total pulse energy density of 2.5 mJ/m^2 (ICNIRP, 2009a). Cooray (2003) has described various mathematical models for return strokes, which are the strongest sources of RF-EMF associated with lightning. Peak electric-field strengths of up to 10 kV/m are possible within 1 km from where the lightning strikes. At distances greater than 100 km, the field strength decreases rapidly to a few volts per metre, with peak dE/dt of about 20 V/m per μs, and then further decreases over a few tens of microseconds. Willett *et al.* (1990) measured the electric-field strength during return strokes as a function of time and conducted Fourier analysis to determine the average spectrum between 200 kHz and 30 MHz. The energy spectral density reduced according to $1/f^2$ at frequencies of up to about 10 MHz and more rapidly thereafter.

1.2.2 Man-made fields

There are numerous different sources of man-made RF fields. The more common and notable man-made sources of radiation in the RF range of 30 kHz to 300 GHz are presented in Fig. 1.6.

Sometimes such fields are an unavoidable consequence of the way systems operate, e.g. in the case of broadcasting and telecommunications, where the receiving equipment is used at locations where people are present. In other situations, the fields are associated with energy waste from a process, e.g. in the case of systems designed to heat materials (ICNIRP, 2009a).

The typical emission characteristics of sources will be summarized here, along with exposure and dose information where available. However, it is important to recognize that fields typically vary greatly in the vicinity of sources and spot measurements reported in the literature may not be typical values. This is because assessments are often designed to identify the maximum exposures that can be reasonably foreseen, e.g. for workers near sources, and to ensure that these do not exceed exposure limits.

(a) Radio and television broadcasting

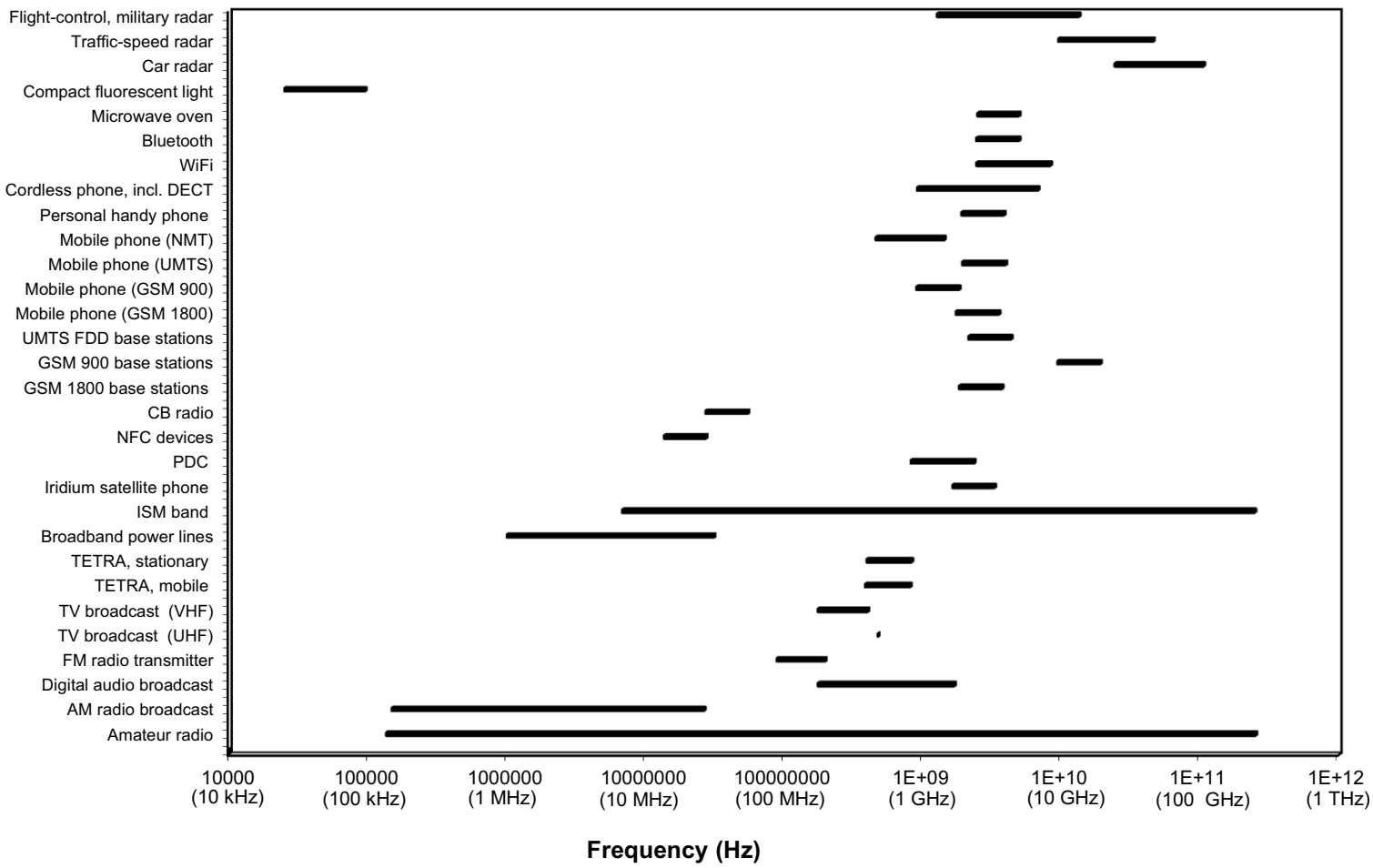
The frequency bands used for broadcasting of radio and television signals are broadly similar across countries and are shown in Table 1.2.

Analogue broadcast radio has been available for many years and uses amplitude modulation (AM) in the long, medium and short-wave bands, but the sound quality is not as good as with frequency modulation (FM) in band II, which became available later and is now more popular for listening. The short-wave band continues to be important for international radio broadcasting, because signals in this frequency band can be reflected from the ionosphere to travel around the world and reach countries thousands of kilometres away (AGNIR, 2003).

Band III was the original band used for television broadcasting and continues to be used for this purpose in some countries, while others have transferred their television services to bands IV and V. Band III is also used for digital audio broadcasting (DAB), exclusively so in countries that have transferred all their television services to bands IV and V. Analogue and digital television transmissions presently share bands III, IV and V, but many countries are in the process of transferring entirely to digital broadcasting (ICNIRP, 2009a).

AGNIR (2003) have described broadcasting equipment in the United Kingdom in terms of

Fig. 1.6 Man-made sources of radiation in the radiofrequency range (30 kHz to 300 GHz)



AM, amplitude-modulated; CB, citizen band; DECT, digital enhanced cordless telecommunications; FDD, frequency-division duplex; FM, frequency-modulated; GSM, Global System for Mobile communications; ISM, industrial, scientific and medical; NFC, near-field communication; NMT, Nordic Mobile Telephony; PDC, personal digital cellular; TETRA, Terrestrial Trunked Radio; TV, television; UHF, ultra-high frequency; UMTS, Universal Mobile Telecommunications System; VHF, very high frequency; WiFi, standard wireless local area network (WLAN) technology.

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Table 1.2 Frequency bands used for broadcasting of television and radio signals

Designation	Frequency range	Usage
Long wave	145.5 – 283.5 kHz	AM radio
Medium wave	526.5 – 1606.5 kHz	AM radio
Short wave	3.9 – 26.1 MHz	International radio
UHF (Bands IV and V)	470 – 854 MHz	Analogue and digital TV
VHF (Band II)	87.5 – 108 MHz	FM radio
VHF (Band III)	174 – 223 MHz	DAB and analogue/digital TV

AM, amplitude modulation; DAB, digital audio broadcasting; FM, frequency modulation; TV, television; UHF, ultra high frequency; VHF, very high frequency
Adapted from AGNIR (2003)

the numbers of transmitters operating at a given power level in each frequency band (Table 1.3). The overall trends are probably similar in other countries and the main change since that time is likely to have been a growth in the number of digital transmitters for radio and television (ICNIRP, 2009a).

(i) Long-, medium- and short-wave bands

Antennae broadcasting in the long- and medium-wave bands tend to be constructed as tall metal towers, with cables linking the towers to each other and to the ground. Often, a single low-frequency (LF) or medium-frequency (MF) radiating structure may involve several closely located towers that are fed in such a way that a directional beam pattern is formed. Some towers are energized and insulated from the ground, while others are grounded and act as reflectors. Transmitters designed to provide local radio services, e.g. around cities, use powers in the range of 100 W to 10 kW, while a small number of transmitters that provide national services over large distances radiate up to a few hundred kilowatts (ICNIRP, 2009a).

The high-frequency (HF) band is used for international broadcasting and comprises wavelengths that are somewhat shorter than those in the long- and medium-wave bands. Curtain arrays, composed of multiple horizontal dipole antennae suspended between towers, are used to form narrow beams directed upwards towards the required azimuth and elevation angles. The beams reflect off the ionosphere and provide services to distant countries without the need for any intermediate infrastructure. Typical curtain arrays can be up to 60 m in height and width, and might, for example, involve 16 dipoles arranged as four vertically stacked rows of four with a reflecting wire mesh screen suspended behind them. Given the transmission distances required, the powers are high, typically around 100–500 kW. The HF band has the fewest transmitters of any of the broadcast bands (ICNIRP, 2009a). Allen *et al.* (1994) reported 25 HF transmitters with powers in the range 100–500 kW and three with powers greater than 500 kW in the United Kingdom.

Broadcast sites can be quite extensive, with multiple antennae contained within an enclosed area of several square kilometres. A building containing the transmitters is generally located on the site and RF feeder cables are laid from this building to the antennae. On HF sites, switching matrices allow different transmitters to be connected to different antennae according to the broadcast schedule. The feeders may be either enclosed in coaxial arrangements or open, e.g. as twin lines having pairs of conductors around 15 cm apart suspended about 4 m above ground level.

In considering reported measurements of RF fields at MF/HF broadcast sites, it is important to note that workers may spend much of their time

Table 1.3 Approximate number of broadcast transmitters in the United Kingdom[a]

Service class	Effective radiated power (kW)					
	0–0.1	> 0.1–1.0	> 1.0–10	> 10–100	> 100–500	> 500
Analogue TV	3496	589	282	122	86	19
DAB	4	126	121	–	–	–
Digital TV	134	177	192	2	–	–
MW/LW radio	14	125	38	19	12	–
VHF FM radio	632	294	232	98	72	–

[a] For TV sites, each analogue channel (e.g. BBC1) or each digital multiplex counts as one transmitter.
DAB, digital audio broadcasting; FM, frequency modulation; LW, long wave; MW, medium wave; TV, television; VHF, very high frequency
Adapted from AGNIR (2003)

in offices, workshops or the transmitter halls. Such locations can be far from the antennae, resulting in exposure levels that are much lower than when personnel approach the antennae to carry out maintenance and installation work.

Jokela *et al.* (1994) investigated the relationship between induced RF currents flowing through the feet to ground and the RF-field strengths from MF and HF broadcast antennae. The MF antenna was a base-fed monopole, 185 m high, transmitting 600 kW at 963 MHz. At distances of 10, 20, 50, and 100 m from the antenna, the electric-field strength at 1 m height was around 420, 200, 60 and 30 V/m, respectively. At the same distances, currents in the feet were around 130, 65, 30 and 10 mA. The HF antenna was a 4 × 4 curtain array suspended between 60 m towers and radiating 500 kW at 21.55 MHz. The total field in front of the antenna at 1 m height ranged from about 32 V/m at 10 m through a maximum of 90 V/m at 30 m, a minimum of 7 V/m at 70 m and thereafter rose to around 20 V/m at distances in the range 100–160 m.

Mantiply *et al.* (1997) have summarized measurements of RF fields from MF broadcast transmitters contained in several technical reports from the mid-1980s to early 1990s from government agencies in the USA. A study based on spot measurements made at selected outdoor locations in 15 cities and linked to population statistics showed that 3% of the urban population were exposed to electric-field strengths greater than 1 V/m, while 98% were exposed to field strengths above 70 mV/m and the median exposure was 280 mV/m. RF-field strengths were also measured near eight MF broadcast antennae, one operating at 50 kW, three at 5 kW and four at 1 kW. The measurements were made as a function of distance along three radials at most of the sites. At distances of 1–2 m, the electric-field strengths were in the range 95–720 V/m and the magnetic-field strengths were in the range 0.1–1.5 A/m, while at 100 m, electric-field strengths were 2.5–20 V/m and magnetic-field strengths were in the range 7.7–76 mA/m.

Mantiply *et al.* (1997) also reported field measurements near short-wave (HF) broadcast antennae. As mentioned earlier, these are designed to direct the beams upwards at low elevation angles. Hence, the field strengths at locations on the ground are determined by sidelobes (see Glossary) from the antennae and they vary unpredictably with distance and from one antenna to another. Measurements were made at four frequencies in the HF band and at six locations in a community around 10 km from an HF site, which was likely to have transmitted 250 kW power. Electric- and magnetic-field strengths at individual frequencies varied in the ranges 1.5–64 mV/m and 0.0055–0.16 mA/m, while the maximum field strengths just outside the site boundary were 8.6 V/m and 29 mA/m.

Field strengths measured at a distance of 100 m along a "traverse" tangential to the beam from a curtain array transmitting at 100 kW were in the ranges 4.2–9.2 V/m and 18–72 mA/m. A final set of measurements was made at a distance of 300 m from another curtain array transmitting at 100 kW, while the beam was steered through ± 25° in azimuth. The field strengths were in the ranges 1.7–6.9 V/m and 14–29 mA/m.

(ii) VHF and UHF bands

The powers used for broadcasting in the VHF and UHF bands vary widely according to the area and terrain over which coverage is to be provided (Table 1.2). UHF transmissions are easily affected by terrain conditions, and shadowed areas with poor signal strength can occur, e.g. behind hills and in valleys. For this reason, in addition to a main set of high-power transmitters, large numbers of local booster transmitters are needed that receive signals from the main transmitters and rebroadcast them into shadowed areas. The main transmitters are mounted at the top of masts that are up to several hundreds of metres high and have effective radiated powers (ERPs) (see Glossary) of up to about 1 MW, while the booster transmitters have antennae that are mounted much nearer to the ground and mostly have powers of less than 100 W. VHF signals are less affected by terrain conditions and fewer booster transmitters are needed.

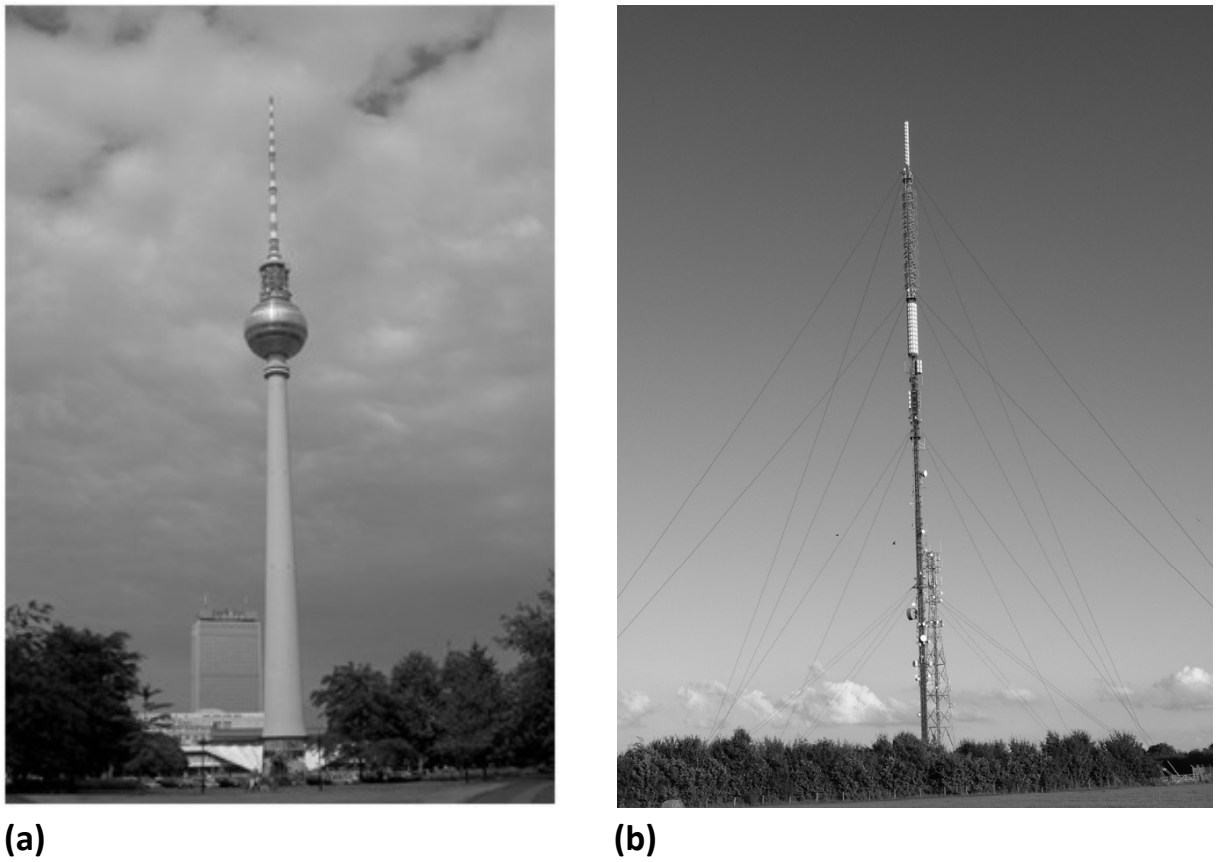
Typical high-power broadcast transmitter masts are shown in Fig. 1.7.

Access to the antennae on high-power VHF/UHF masts is gained by climbing a ladder inside the tower; reaching the antennae at the top involves passing in close proximity to radiating antennae at lower heights. The VHF transmissions have wavelengths of similar dimensions to the structures that form the tower itself, e.g. the lengths of the steel bars or the spaces between them, and hence tend to excite RF current flows in these items. Standing waves (see Glossary) can be present within the tower, and the measured field strengths can be strongly affected by the presence of a person taking measurements. Thus, measurements of field strength can seem unstable and difficult to interpret. Currents flowing within the body can be measured at the wrist or ankle and these are more directly related to the specific absorption rate (SAR; dose) in the body than the fields associated with the standing waves. Hence, it can be preferable to measure body current (see Section 1.3) rather than field strength on towers with powerful VHF antennae.

Several papers discussed by ICNIRP (2009a) have reported measurement results in the range of tens to hundreds of volts per metre within broadcast towers, but it is not clear how representative these spot measurements are of typical worker exposures. Cooper *et al.* (2004) have used an instrument worn on the body as personal dosimeter to measure electric- and magnetic-field strengths during work activities at a transmitter site. They reported that a wide temporal variation in field strengths was typically found within any single record of exposure to electric or magnetic fields during work on a mast or tower used for high-power VHF/UHF broadcasts. Fig 1.8 shows a typical trace that was recorded for a worker during activities near the VHF antennae while climbing on a high-power VHF/UHF lattice mast. The field strength commonly ranged from below the detection threshold of about 14 V/m to a level approaching or exceeding the upper detection limit of about 77 V/m. The highest instantaneous exposures usually occurred when the subject was in the vicinity of high-power VHF antennae or when a portable VHF walkie-talkie radio was used to communicate with other workers.

Field strengths around the foot of towers/masts have also been reported and seem quite variable. Mantiply *et al.* (1997) described values in the range of 1–30 V/m for VHF television, 1–20 V/m for UHF television and 2–200 V/m for VHF FM radio sites. Certain designs of antennae have relatively strong downward-directed sidelobes,

Fig. 1.7 Typical antenna masts for power broadcasting of radio and television signals



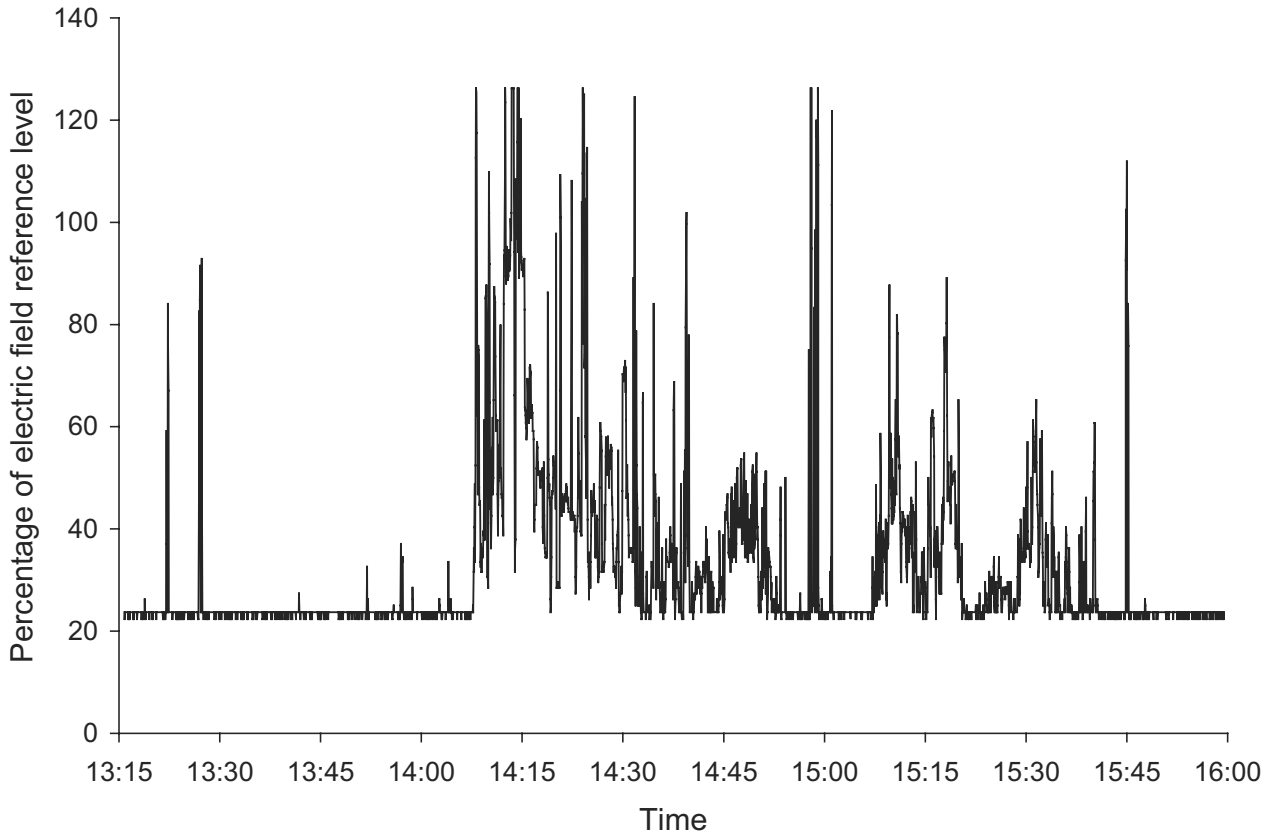
(a) A concrete tower, 368 m high, with a spherical structure at just above 200 m. This is accessed by lifts from ground level and contains various equipment as well as a public restaurant. The radiating antennae are above the sphere and the antennae operating at the highest frequencies are nearest to the top. Multiple dipole antennae protrude through the wall of the red/white cylinder to provide FM radio services in band II, and television and DAB services in band III. Contained within the top-most section of the tower are the band IV and V antennae for more television services.
(b) A steel-lattice tower with the television antennae in the white cylinder at the top. Antennae for VHF and DAB broadcast radio services are mounted on the outside of the tower just below the television antenna and there are multiple antennae for other communications purposes at lower heights. The transmitters are in a building near the base of the tower and the coaxial cables carrying the RF to the transmitting antennae pass up inside the tower.
Courtesy of the Health Protection Agency, United Kingdom

known as grating lobes, which is a possible explanation for such variability.

VHF/UHF broadcast antennae are designed to direct their beams towards the horizon, usually in all directions around the tower. Hence, field strengths at ground level and in communities near the tower are much lower than at comparable distances within the beam. When the beams do eventually reach ground level, they have spread out considerably, again implying that exposures for the general public are substantially lower than those for workers at locations to which they have access, as summarized above (ICNIRP, 2009a).

Mantiply *et al.* (1997) report studies of population exposure in the USA conducted during the 1980s and based on spot measurements at selected outdoor locations. An estimated 50%, 32% and 20% of the population were exposed at greater than 0.1 V/m from VHF radio, VHF television and UHF television signals, respectively. VHF radio and television caused exposures to 0.5% and 0.005% of the population at greater than

Fig. 1.8 Relative electric-field strength recorded for an engineer operating on a mast supporting antennae for high-power VHF/UHF broadcast transmissions



The reference level is 61 V/m, as taken from the ICNIRP (1998) exposure guidelines for workers over the relevant frequency range (10–400 MHz).
UHF, ultra high frequency; VHF, very high frequency
From Cooper *et al.* (2004). By permission of Oxford University Press.

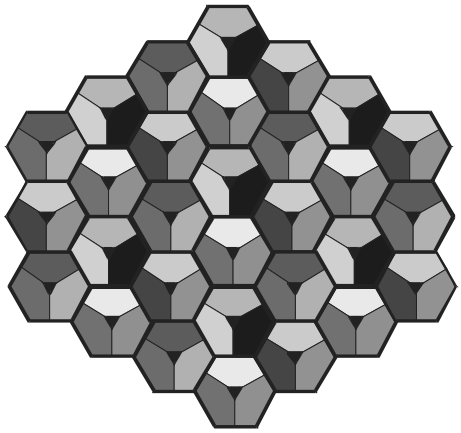
2 V/m, while UHF television caused exposure to 0.01% of the population at greater than 1 V/m.

Field strengths associated with VHF/UHF radio and television broadcast signals were measured at 200 statistically distributed locations in residential areas around Munich and Nuremberg in Germany (Schubert *et al.*, 2007). The aim of the study was to investigate whether the levels had changed as a result of the switch-over from analogue to digital broadcasting, and measurements were made before and after this change occurred at each location. The median power density was 0.3 μW/m^2 (11 mV/m) for the analogue signals and 1.9 μW/m^2 (27 mV/m) for the digital signals. FM radio signals had median power densities of 0.3 μW/m^2 (11 mV/m), similar to the analogue television signals, and the values ranged over approximately two orders of magnitude on either side of the medians for all types of broadcast signal. It is interesting to note that these values seem to be lower than those reported in the USA during the 1980s.

(b) Cellular (mobile-phone) networks

Unlike broadcasting, for which high-power transmitters are used to cover large areas extending 100 km or more from the transmitter, cellular networks employ large numbers of low-power transmitters, known as base stations, which are scattered throughout an area where coverage

Fig. 1.9 Example of a coverage plan for a cellular network



Each cell is hexagonal, with a base station at its centre and configured to provide signals over three sectors of 120 degrees. The shading show how coverage is provided everywhere by use of 12 frequency channels, none of which are used in the adjacent cells.
Courtesy of the Health Protection Agency, United Kingdom

is to be provided. This is because communications are two-way (duplex) in cellular networks, with each user requiring their own dedicated communication channels, both for the uplink (phone to base station) and for the downlink (base station to the phone). Each base station has limited capacity in terms of the number of calls it can serve simultaneously, so the transmitters are closer together in locations where there is a high density of users. For example, the transmitters may be about 10 km apart in sparsely populated areas, but 100 m or less apart in city centres.

An important consideration in the design of cellular networks is that operators have a limited spectrum window available and have to reuse their frequency channels to provide coverage everywhere. A typical frequency map illustrating how coverage can be provided with 12 frequency channels is shown in Fig. 1.9. Signals that use the same frequency in different cells can potentially interfere with each other, but the signal strength diminishes with increasing distance from base stations and frequencies are not reused in adjacent cells/sectors. Hence, services can be provided without interference, provided that the radiated powers of phones and base stations are minimized during calls. This principle has important consequences for the RF exposures of people using phones and living near base stations (ICNIRP, 2009a).

Developments in mobile-phone technology are broadly categorized according to four different generations (Table 1.4). The first-generation networks (1G) were rolled-out in the mid-1980s and included Advanced Mobile Phone System (AMPS) in North America, Total Access Communication Systems (TACS) in much of Europe, Nippon Telegraph and Telephone (NTT) in Japan, and Nordic Mobile Telephony (NMT) in Scandinavia. The systems were based on analogue technology and used frequency modulation to deliver voice-communication services. These networks mostly closed down from around the year 2000, as users moved to later generations of the technology (ICNIRP, 2009a).

Second-generation networks (2G) were established in the early 1990s and continue to operate. They are based on digital technology and use voice coding to improve spectral efficiency. Many systems use time-division multiple access (TDMA) within their frequency channels and such systems include Global System for Mobile (GSM) in Europe, Personal Digital Cellular (PDC) in Japan, and both Personal Communication Systems (PCS) and D-AMPS (digital AMPS, also known as "TDMA") in North America. Other north-American systems are known as CDMA, because they use code-division multiple access. 2G systems were extended to include some basic data services, but subsequent systems with enhanced data services were usually termed 2.5G (ICNIRP, 2009a).

The third generation of mobile phones (3G), with comprehensive data services, became available in the early 2000s. These phones have developed to become today's "smartphones," although it is important to recognize that they are fully backward-compatible with 2G networks and whether 2G or 3G is used at any given time

Table 1.4 Frequency bands originally used by different mobile-phone systems

Generation	Start date of commercial availability[a]	Main geographical region	System[b]	Handset band (MHz)	Base-station band (MHz)	Channel spacing (kHz)
1	1981	Nordic countries	NMT450	453.5 – 457.5	463.5 – 467.5	25
	1986		NMT900	890 – 915	935 – 960	12.5
	1985	Europe	TACS/ETACS	872 – 915	917 – 960	25
	1989	Japan	JTACS/NTACS	898 – 925	860 – 870	25/12.5
	1985	Germany	NET-C	451.3 – 455.74	461.3 – 465.74	20
	1985	USA & Canada	AMPS	824 – 849	869 – 894	30
	1985		N-AMPS	824 – 849	869 – 894	10
	1987	Japan	NTT	925 – 940	870 – 885	25
2	1992	USA & Canada	TDMA800	824 – 849	869 – 894	30
	1998		TDMA1900	1850 – 1910	1930 – 1990	30
	1992	Europe	GSM900	890 – 915	935 – 960	200
	1993		GSM1800	1710 – 1785	1805 – 1880	200
	2001	USA & Canada	GSM1900 (PCS)	1850 – 1910	1930 – 1990	200
	1993	Japan	PDC800	940 – 956	810 – 826	25
	1994		PDC1500	1429 – 1465	1477 – 1513	25
	1998	USA & Canada	CDMA800	824 – 849	869 – 894	1250
	1997		CDMA1900	1850 – 1910	1930 – 1990	1250
3	2001	World	IMT-2000 (W-CDMA)	1920 – 1980[c]	2110 – 2170[c]	5000
4		World	LTE	Many possible	Many possible	Various

[a] The start dates of use will be different depending on country.
[b] For abbreviations, see Cardis *et al.* (2011b) and Singal (2010).
[c] Technical standards for a 2001 version for the 3G systems (IMT-2000). Note that standards for the 3G systems evolve quickly.
Compiled by the Working Group and adapted mainly from the references mentioned in footnote b

depends on network coverage and how operators have chosen to manage call/data traffic within their network. The systems use CDMA radio-access methods (ICNIRP, 2009a).

A fourth generation (4G) of the technology is just starting to be rolled out to meet the increasing demand for data services. Some systems are known as Long-term Evolution (LTE) and use orthogonal frequency-division multiplexing (OFDM), while others are based on Worldwide Interoperability for Microwave Access (WiMax). As with 3G services, this technology will be overlaid on other services, and phones will be able to support multiple access modes (4G, 3G and 2G) (Buddhikot *et al.*, 2009).

The frequency bands originally used by cellular networks in various parts of the world are shown in Table 1.4. It is important to note that spectrum liberalization is ongoing at present, such that operators who hold a license for a particular part of the spectrum may choose to use it to provide services with any technology they wish. For example, bands originally reserved for 2G services such as GSM are being made available for 3G/4G services in many countries as demand shifts from 2G to systems with more capacity for data services. Also, with the move to digital-television broadcasting, the spectrum in the frequency range of 698 to 854 MHz is becoming available and being reallocated to 3G/4G cellular services (Buddhikot *et al.*, 2009).

(i) Mobile-phone handsets

The output powers and – where TDMA is used – the burst characteristics of various types of mobile phones are summarized in Table 1.5. Analogue mobile phones were specified to have maximum equivalent isotropically radiated powers (EIRP) of 1 W, but the antennae were not isotropic and would have had gains of around 2 dB. This implies the radiated powers would have been around 600 mW. 2G mobile phones that use TDMA have time-averaged powers that are less than their peak powers according to their duty factors, i.e. the time they spend transmitting, as a proportion of the total. For example, GSM phones that transmit at a power level of 2 W in the 900 MHz band (GSM900) have time-averaged powers that are 12% of this, i.e. 240 mW. Maximum time-averaged output powers are generally in the range of 125–250 mW for 2G onwards.

Mobile phones are generally held with their transmitting antennae around 1–2 cm from the body, so the RF fields they produce are highly non-uniform over the body and diminish rapidly in strength with increasing distance. The fields penetrate body tissues, leading to energy absorption, which is described by the SAR. SAR values are derived by phone manufacturers under a series of prescribed tests and the maximum value recorded under any of the tests is reported in the product literature. Values in normal usage positions should be lower than the values declared by manufacturers because the positions used in the testing standards are designed to mimic near-worst-case conditions.

While Table 1.5 gives maximum output powers for phones, the actual power used at any point during a call is variable up to this maximum. As mentioned above, to minimize interference in the networks, the power is dynamically reduced to the minimum necessary to carry out calls. Vrijheid *et al.* (2009a) found that the reduction was on average to around 50% of the maximum with GSM phones, whereas Gati *et al.* (2009) reported that 3G phones only operated at a few percent of the maximum power.

Another consideration is that GSM phones employ a mode called discontinuous transmission (DTX), under which their transmission-burst pattern changes to one with a lower duty factor during the periods of a conversation when the mobile-phone user is not talking. Wiart *et al.* (2000) found that DTX reduced average power by about 30% for GSM phones.

(ii) Time trends in SAR for mobile phones

As shown in Table 1.5, analogue mobile phones had higher specified maximum radiated powers than digital ones (typically 0.6 W versus 0.1–0.25 W). While these systems are no longer in use and few data on exposure are available, it is of interest to consider whether exposures from these phones would have been higher than with present-day phones. Key differences, aside from relative power levels, are that analogue phones were larger than their modern digital counterparts and that they generally had larger antennae, e.g. extractable whip antennae rather than the compact helices and patch antennae used nowadays. The increased distance between the antenna and the head would have reduced the SAR level overall, and the larger size of the antenna would have led to a more diffuse distribution of SAR in the head.

The evolution of localized SAR values over time is also interesting to consider. Cardis *et al.* (2011b) assembled a database of reported peak 1-g and 10-g SARs for phones from a range of publications and web sites. Most data covered the years 1997–2003, and no significant upward or downward trends over this time period were found for the 900 MHz or 1800 MHz bands.

In summary, the peak spatial SARs (psSAR) do not seem to have changed significantly over time as analogue phones have been replaced by digital ones. However, the more diffuse nature of the distributions produced by analogue phones

Table 1.5 Output powers and TDMA characteristics of various types of mobile phone

System	Peak power (W)		Burst duration (ms)	TDMA duty factor	Average power (W)
	EIRP	Output			
GSM900	-	2.0	0.5769	0.12	0.24
GSM1800	-	1.0	0.5769	0.12	0.12
PCS1900	-	1.0	0.5769	0.12	0.12
NMT450	1.5	0.9	-	NA	0.9
PDC	-	0.8	3.333 or 6.666	1/6 or 1/3	0.133 or 0.266
NMT900	1.0	0.6	-	NA	0.6
TACS/ETACS	1.0	0.6	-	NA	0.6
AMPS/NAMPS	1.0	0.6	-	NA	0.6
TDMA800	-	0.6	6.666	1/3	0.2
TDMA1900	-	0.6	6.666	1/3	0.2
CDMA800	-	0.25	-	NA	0.25
CDMA1900	-	0.25	-	NA	0.25
IMT-2000	-	0.25	-	NA	0.25

EIRP, equivalent isotropically radiated power; NA, not applicable; TDMA, time-division multiple access
Compiled by the Working Group

would likely have led to a greater overall SAR in the head, including the brain.

(iii) Phones not making calls

The emitted powers from phones when they are on standby and not making calls are also of interest. Systematic studies have not been published on this topic, but transmissions under these conditions are brief and infrequent, and exposure is expected to be very small when averaged over time.

Phones equipped for data services such as e-mail will transmit for longer time periods than ordinary phones because they will be checking e-mail servers and synchronizing databases held on the phone with those on remote servers. Also, uploading large files such as videos and photographs may take many minutes. The phone is unlikely to be held against the user's head while this is taking place, although it may be in the user's pocket or elsewhere on the body, which may lead to local emissions at a higher power level than during calls, e.g. if general packet radio service (GPRS) is used, involving multislot transmission with GSM.

The sending of a text message from a mobile phone involves a short period of transmission. Gati *et al.* (2009) showed that a long text message would take at most 1.5 seconds to send with GSM systems.

(iv) Hands-free kits and Bluetooth earpieces

A phone may sometimes be used with a wired hands-free kit, in which case parts of the body other than the head may be exposed to maximal localized SARs, e.g. if the phone is placed in the user's pocket during the call. While one might expect that the audio cable to the ear-piece would not efficiently guide RF fields to the ear-piece, and that the use of wired hands-free kits would lead to greatly reduced SARs in the head due to the increased distance of the phone from the head, there have been suggestions that this is not always the case.

Porter *et al.* (2005) showed that the layout of the cables of the hands-free kit was a critical factor in determining head exposures and that certain geometries could result in appreciably more power being coupled into the audio cable than others. However, in all of the combinations

tested, the maximum value for SAR 10 g was lower when a hands-free kit was used than when it was not. Kühn *et al.* (2009a) further developed procedures for the testing of hands-free kits under worst-case and realistic conditions of use and applied them to a set of phones and kits. The authors concluded that exposure of the entire head was lower when a hands-free kit was used than when the phone was held directly against the head, but that there might be very localized increases in exposure in the ear.

Wireless hands-free kits are available that use the Bluetooth RF communications protocol to link to a mobile-phone handset located within a few metres of the body. This protocol provides for RF transmissions in the frequency range 2.4–2.5 GHz at power levels of 1, 2.5 or 100 mW. Only the lowest of these power levels would be used with a wireless hands-free kit and these are around a hundred times lower than the maximum output powers of mobile phones. In the study on wired hands-free kits mentioned above, Kühn *et al.* (2009a) also tested Bluetooth wireless hands-free kits and concluded that they are responsible for a low but constant exposure.

(v) Mobile-phone base stations

The base stations that provide mobile-phone services to come in many different sizes and shapes, according to their individual coverage requirements.

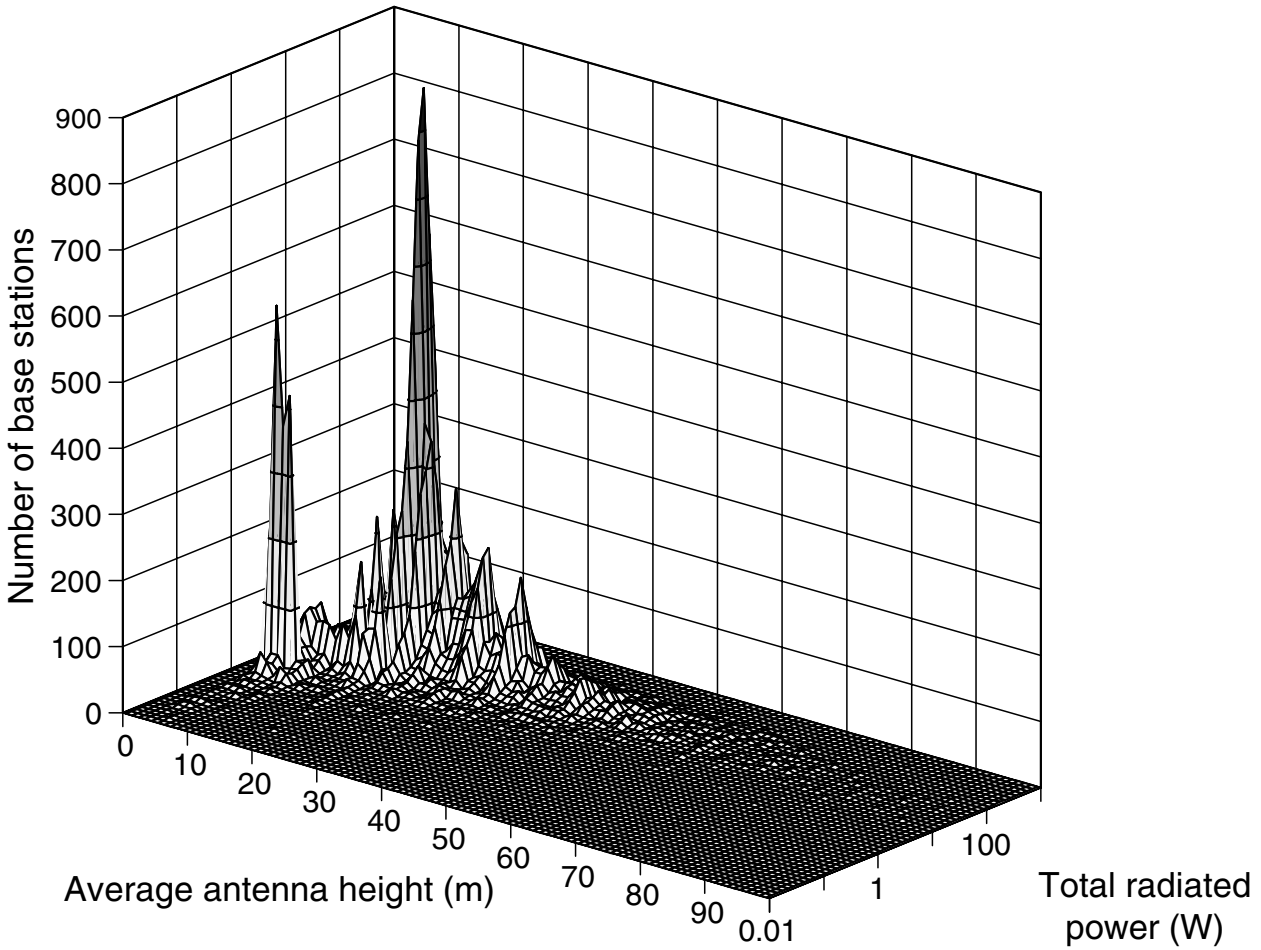
The radiated powers and heights of mobile-phone base-station antennae are highly variable. Cooper *et al.* (2006) collected data on base-station antenna height and power from all cellular operators in the United Kingdom, a total of 32 837 base stations, for the year 2002. The data are presented in Fig. 1.10 and show that base-station powers typically vary from about 0.1 W to 200 W and that heights range from about 3 m to 60 m above ground level. There is a large group of base stations with heights in the range 15–25 m and powers in the range 20–100 W, and a second group with heights in the range 2–6 m and powers of about 2 W. Cooper *et al.* concluded that the base stations in the first group are likely to serve macrocells and provide the main coverage for cellular networks, while those in the second group are likely to be microcells and provide a second layer of coverage, e.g. in densely populated areas.

Numerous spot measurements have been carried out to determine levels of exposure in the vicinity of mobile-phone base stations, often within national campaigns to address public concerns. Generally, these spot measurements take into account exposure contributions from all signals in the bands used by the base station at the time of measurement, but ignore other parts of the spectrum, such as those used by broadcast transmitters. Mann (2010) summarized the United Kingdom audit programme, which encompassed 3321 measurements at 541 sites comprising 339 schools, 37 hospitals and 165 other locations. Exposure quotients, describing the fraction of the ICNIRP general public reference level (ICNIRP, 1998) that is contributed collectively by the signals measured, are shown in Fig. 1.11 as a cumulative distribution.

Fig. 1.11 includes a log-normal curve fitted optimally (least squares) to the data. The curve suggests that the data are approximately log-normally distributed, although with a longer tail towards the lower values. The quotient values are 8.1×10^{-6} (3.0×10^{-8} – 2.5×10^{-4}), where the first figure is the median value and the values in parentheses indicate the range from the 5th to the 95th percentile. About 55% of the measurements were made outdoors and these were associated with higher exposure quotients than the indoor measurements. The median quotients for the outdoor and indoor measurements were 1.7×10^{-5} and 2.8×10^{-6} respectively, i.e. the outdoor median was around six times higher than the indoor median (Mann, 2010).

The exposure quotients may be converted to electric-field strengths or power densities by assuming a value for the reference level, but the

Fig. 1.10 Distribution of 32 837 base stations in the United Kingdom according to average antenna height and total radiated power



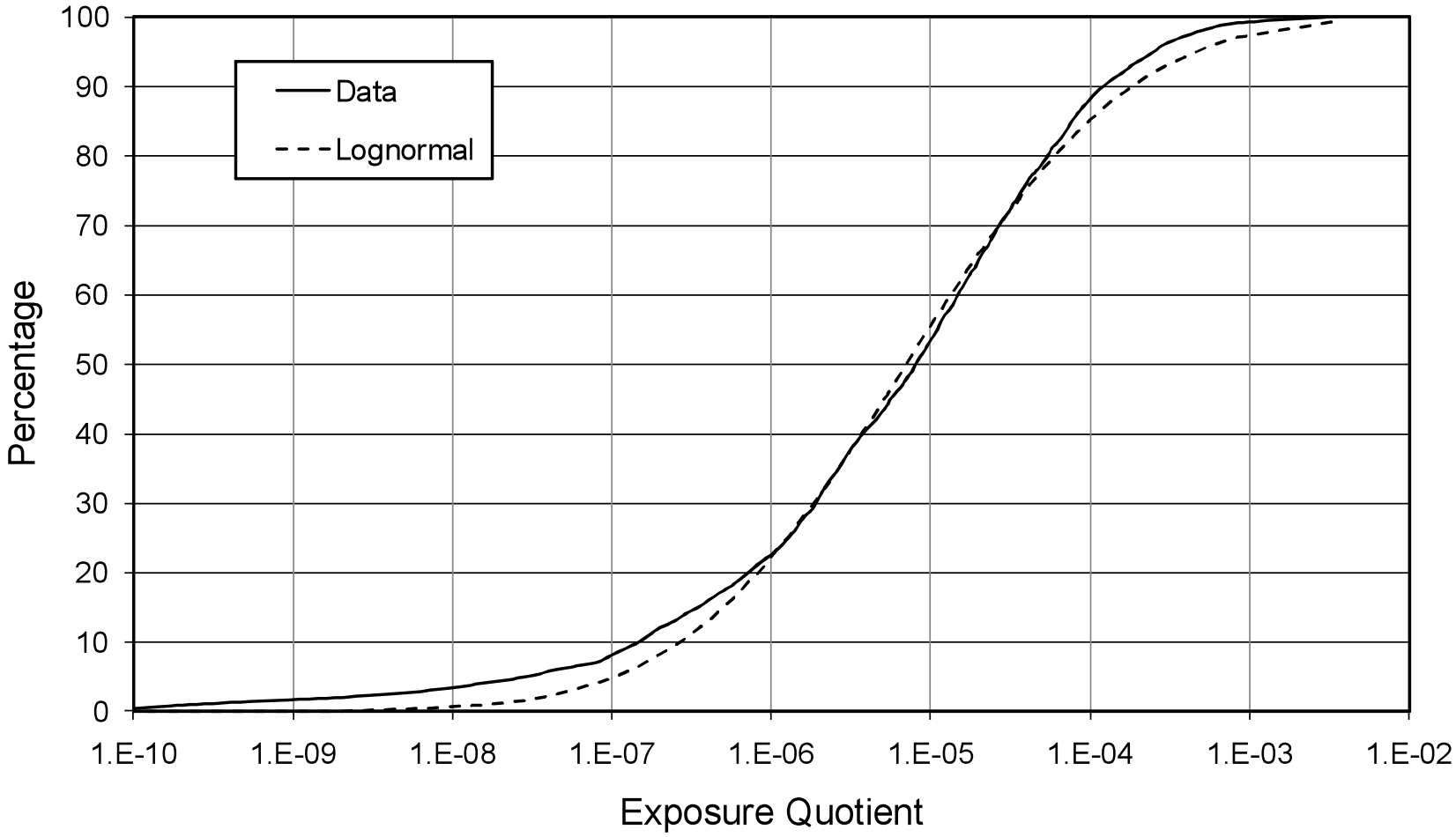
Antenna height is given as an average value since some base stations with multiple antennae have the antennae mounted at different heights. From Cooper *et al.* (2006)

latter varies from 2 to 10 W/m^2 over the frequency range considered in the measurements (TETRA at 390 MHz to UMTS at 2170 MHz). The variation of the reference level is, however, very much less than the variation in the exposure quotients, so taking 4.5 W/m^2 as the reference level (the value at 900 MHz) still yields useful data. The power densities and electric-field strengths based on this assumed value are shown in Table 1.6.

Table 1.6 shows electric-field strengths that range from about ten to a few hundred millivolts per metre indoors, where people spend most of their time. However, in considering these data it is important to recognize that the indoor sites in this study were selected according to public concern regarding a nearby base station; these field strengths may thus be higher than would be found at locations representative of exposure of the general population.

Petersen & Testagrossa (1992) published measurements of power densities around analogue base-station sites in the USA, transmitting in the frequency range 869–894 MHz. A basic start-up site would serve a cell with a range of up to 12–16 km and provide up to 16 signals (each serving one phone call) from a

Fig. 1.11 Cumulative distribution of exposure quotients corresponding to 3321 spot measurements made by Office of Communications at 499 sites where public concern had been expressed about nearby base stations



The exposure quotients were calculated by dividing the power density of each individually measured signal by the general public reference level at its frequency according to ICNIRP (1998) and then summing these individual signal quotients to obtain a total quotient of the reference level. The figure shows a log-normal curve fitted to the data.
From Mann (2010).

Table 1.6 Summary of exposure quotients measured in the United Kingdom

Category	No. of measurements	Exposure quotient ($\times 10^{-6}$)		Power density ($\mu W/m^2$)		Electric-field strength (mV/m)	
		Median	Range[a]	Median	Range[a]	Median	Range[a]
All data	3321	8.1	0.03 – 250	37	0.13 – 1100	120	7.1 – 650
Outdoor	1809	17	0.052 – 314	77	0.23 – 1400	170	9.3 – 730
Indoor	1516	2.8	0.024 – 124	13	0.11 – 560	69	6.4 – 460

[a] Range from 5th to 95th percentiles

These data are from an audit of base stations up to the end of 2007. Equivalent power densities and electric-field strengths are given assuming a reference level of 4.5 W/m^2.

Adapted from Mann (2010)

single omni-directional antenna. As demand grew, sites could be expanded to split cells into three sectors with up to six antennae mounted on a triangular mast head. Again, each antenna would provide up to 16 signals, so there would be a maximum of 96 signals available, 32 of which would have been directed into each sector. Values for nominal ERP (see Glossary) were about 100 W and so the radiated power would have been of the order of 10 W per signal from omni-directional and sectored sites, with typical antenna gains in the range of 9–10 dB and 8–12 dB, respectively.

For four masts ranging from 46 to 82 m in height, measurements were made at intervals along radials from the bases of the masts out to distances of a few hundred metres. Individual signals from a given antenna were found to vary in strength at any given measurement position and the sidelobe structure of the antenna was evident in that the signal strength had an oscillatory dependence on distance. The maximum power density per signal was < 100 $\mu W/m^2$, except in proximity to metal structures near the foot of the tower. Thus, even for 96 signals transmitted simultaneously, the maximum aggregate power density possible would have been < 10 mW/m^2.

Henderson & Bangay (2006) reported on a survey of exposures around 60 base station sites in Australia transmitting CDMA800 (29 sites), GSM900 (51 sites), GSM1800 (12 sites) and 3G UMTS (35 sites) signals. Initially, computer modelling was carried out to identify the direction from the mast where maximum exposures were expected. Measurements were then made at distances of 50, 200 and 500 m, and further measurements were then made at the distance where maximum exposures were predicted, which varied from 14 to 480 m from the mast as a consequence of antenna height, pattern and tilt. The maximum recorded power density of 7.8 mW/m^2 corresponded to an exposure quotient of 0.002 (0.2%) relative to the ICNIRP public reference level (identical to the Australian standard at the frequencies concerned). The cumulative distributions also reported in this paper showed roughly similar median exposure quotients of about 0.0015 at 50 and 200 m, 0.0001 at 500 m and 0.004 at the maximum.

The study by Cooper *et al.* (2006) mentioned above focused on measurements around 20 GSM base stations with powers < 5 W and heights < 10 m, selected randomly from all base stations in the United Kingdom. From the total of 32 837 base stations, 3008 eligible stations were identified. The antennae of the selected base stations were often fixed to the walls of buildings at a minimum height of 2.8 m. Theoretical calculations based on the radiated powers showed that the minimum height at which the reference level could be reached was 2.4 m above ground. Exposure measurements were made as a function of distance at 10 of the 20 sites and at 610 locations in total, ranging from 1 to 100 m from the antenna. The highest spot measurement at

an accessible location represented 8.6% of the reference level and the exposures more generally ranged from 0.002% to 2% of the ICNIRP public reference level. Empirical fits showed that the exposure quotients decreased in a way that was inversely proportional to the distance, for distances up to about 20 m from the antennae and thereafter diminished with the fourth power of distance. Exposures close to microcell base stations were found to be higher than close to macrocell base stations, because the antennae were at lower heights and could be approached more closely by the public.

Kim & Park (2010) made measurements at 50 locations between 32 and 422 m from CDMA800 and CDMA1800 base stations in the Republic of Korea. The base stations were selected to represent locations where concern had been expressed by the local population. The highest reported electric field level was 1.5 V/m, equivalent to an exposure quotient of 0.0015 (0.15%) compared with the reference level, and the median exposure quotient was below 0.0001 (0.01%).

The most recent studies have used personal-exposure meters worn for periods of up to several days by groups of volunteers. These studies are covered in Section 1.6.1, and provide information not only on exposure from base stations, but also from other environmental transmitters during typical activities.

(vi) Terrestrial Trunked Radio (TETRA)

TETRA is a cellular radio system designed to meet the needs of professional users and emergency services. The handsets can be used like mobile phones, but are normally used as walkie-talkies, held in front of the face and in push-to-talk (PTT) mode. Remote speaker microphones and a variety of covert add-ons are also available. When the handsets are used with accessories, the transmitting handset may be mounted on the belt, on the chest, or elsewhere on the body. Systems for use in vehicles with the transmitting antennae mounted externally are also available. The operating principles and the detailed characteristics of the signals involved are described in a review by AGNIR (2001).

Several frequency bands are available between 380 and 470 MHz, as well as one set of bands near 900 MHz. Handsets can have peak emitted powers of 1 W or 3 W, while vehicle-mounted transmitters can have powers of 3 W or 10 W. Base stations have similar powers to those used for mobile-phone networks, i.e. a few tens of watts. The system uses TDMA, although the frame rate is slower than that of the TDMA systems involved with mobile phones. There are four slots per frame and 17.6 frames per second. Hence, the bursts from handsets occupy slots with a duration of 14.2 ms and the time-averaged power is a quarter of the peak powers mentioned earlier in this paragraph. The base stations transmit continuous signals AGNIR (2001).

The AGNIR review refers to SARs measured from 1 W and 3 W handsets held to either side of the head and in front of the face in a model of the head. With spatial averaging over 10 g, as per ICNIRP and IEEE exposure guidelines, the 1 W radio produced SARs of 0.88, 0.89 and 0.24 W/kg on the left, right and front of the face, respectively, while the 3 W radio produced SARs of 2.88, 2.33 and 0.53 W/kg, respectively, under the same conditions.

Dimbylow *et al.* (2003) developed a numerical model of a commercially available TETRA handset and calculated SARs in an anatomically realistic numerical model (resolution, 2 mm) of the head developed from MRI images. The handset was modelled as a metal box of dimensions 34 × 50 × 134 mm, and with either a helical (pitch, 4 mm; diameter, 8 mm) or a monopole antenna mounted on its top face, and resonant at 380 MHz. For the handset held vertically in front of the face in the position that was considered to be most representative of practical use, the averaged SARs at 10 g were 1.67 W/kg and 2.37 W/kg per watt of radiated power with the monopole and helical antennae, respectively. Various positions

were considered with the handset held to the sides of the head and the maximum SARs with the two antennae were 2.33 and 3.90 W/kg per watt. These values suggest SARs with 3 W handsets (3/4 W time-averaged) having a helical antenna could exceed the 2 W/kg restriction on exposure for the general public, if the handsets were to transmit at full power for 6 minutes while held to the side of the head.

(vii) Cordless phones

Cordless phones are used to make voice calls and are held against the head just like mobile phones. Hence, the antenna inside the phone is in close proximity to the head and its radiated fields deposit energy inside the head tissues near to the phone, in a similar way to the fields from mobile phones. With cordless phones, communications are made over shorter distances than with mobile phones and so the radiated powers used are lower, but cordless phones do not use adaptive power control, which means that, unlike mobile phones, they do not continually adapt their radiated power to the minimum necessary for satisfactory communication (ETSI, 2010).

With simple cordless installations, the phones are typically placed back on a desk or charging point after a call has finished. However, there are also more complicated installations in which multiple base stations are installed throughout a building and the phones are carried by the user as a personal phone. The radio communications are over distances of a few tens of metres and to the nearest base station, which provides the link into the main wired telephone system.

The first cordless phones used analogue technology and operated to a range of different technical standards, with continuous emitted power levels of about 10 mW during calls. Frequencies were generally in the range 30–50 MHz and therefore about 20 times lower than the frequencies used by mobile phones. Some phones used telescopic antennae of about 15–30 cm in length, while others used helical antennae of about 5 cm in length. The lower frequencies and the greater size of the antennae used with analogue cordless phones would have resulted in a smaller proportion of the radiated power being absorbed, and also in a more diffuse pattern of absorption in the head than occurs with mobile phones (ETSI, 2010).

Modern cordless phones use digital technology, including the digital enhanced cordless telecommunications (DECT) technical standard, which operates in the frequency band 1880–1900 MHz and is the main system used in Europe. In other parts of the world, systems operating around 900, 2400 and 5800 MHz are used as well as DECT (ETSI, 2010).

DECT systems produce discontinuous emissions due to their use of TDMA. The signals from the phone and base station during calls are in the form of 100 bursts every second, each of about 0.4 ms in duration. These bursts are emitted at a peak power level of 250 mW, but the time-averaged power is 10 mW because each device only transmits for 1/24 of the time (duty factor of 4%). Handsets do not transmit unless calls are being made, but when on "standby" most base stations produce 100 beacon pulses per second, each pulse being 0.08 ms in duration. This implies a duty factor of 0.8% (ETSI, 2010).

(viii) Professional mobile radio systems

A variety of professional mobile radio systems, also called private mobile radio (PMR), have been developed over the years and these are generally licensed to professional users by spectrum-management agencies in the countries where they are used. In many countries, the emergency services (police, fire, ambulance, etc.) are converting to the use of digital cellular systems, such as TETRA, although analogue systems – which were the norm before roll-out of TETRA systems – are also used.

The PMR systems use frequencies in the VHF and UHF parts of the spectrum; VHF generally propagates further for a given radiated power

and is, therefore, preferred for longer-distance communications. On the other hand, UHF systems have smaller antennae and present as more compact terminals.

Systems exist in the form of walkie-talkies that are held in front of the face and used in push-to-talk (PTT) mode; they may be built into vehicles with external, e.g. roof-mounted, antennae or be worn on the body. The transmitting antennae can be on the handset itself, on the vehicle, or carried on the chest or waist. The radiated powers are typically in the range 1–5 W, but it is important to take into account the duty factor associated with how they are used: the PTT mode will involve only a few seconds of transmission during the time that the button is pressed down and the user is speaking.

(c) Wireless networks

Wireless networking has developed rapidly since about 2000 and is becoming the method of choice for connecting mobile devices such as laptop computers and mobile phones to other electronic systems and to the Internet. The networks are found in homes, schools, public places such as cafés and transport hubs, and in the workplace. The systems operate to the IEEE802.11 family of technical standards and are often known as "Wi-Fi," after the Wi-Fi Alliance, an organization that certifies inter-operability of devices on the market.

The original version of IEEE802.11 was published in 1997 and provided for data-transfer rates of up to 2 Mbit/s through frequency channels between 2.4 and 2.5 GHz. Subsequent developments using this band were IEEE802.11b and IEEE802.11 g, allowing for rates up to 11 and 54 Mbit/s, respectively. Several frequency bands between 5 and 6 GHz are exploited by IEEE802.11a and provide for 54 Mbit/s communications. The latest devices operate according to IEEE802.11n and provide up to 72 Mbit/s in a single frequency channel, but the standard allows for devices that can use multiple frequency channels simultaneously to deliver much higher data rates (ICNIRP, 2009a).

The IEEE802.11 standard specifies maximum radiated powers, but these are above the values permitted by regulatory agencies in many parts of the world. For example, in Europe the technical standards EN300328 and EN301893 limit the EIRP to 100 mW in the 2.4-GHz band and 200 mW in the 5 GHz band, respectively. Peyman *et al.* (2011) measured the actual power radiated by a selection of Wi-Fi devices marketed among schools in the United Kingdom. The spherically integrated radiated power (IRP) ranged from 5 to 17 mW for fifteen laptops in the 2.45 GHz band and from 1 to 16 mW for eight laptops in the 5 GHz band. For practical reasons and because access points are generally wall-mounted with beams directed into the room, their powers were integrated over a hemisphere. These ranged from 3 to 28 mW for twelve access points at 2.4 GHz and from 3 to 29 mW for six access points at 5 GHz. Thus the radiated powers of laptops seem to range from a few mW up to about 30 mW. In principle, these measurements imply that the powers of access points could range from a few mW up to around 60 mW, if their patterns extend symmetrically into the unmeasured hemisphere, which seems unlikely.

The RF emissions from Wi-Fi devices are in the form of short bursts containing portions of the data being transmitted and other information, such as acknowledgements that data have been successfully received. Unlike the emissions from mobile phones using TDMA, the bursts are irregular in terms of timing and duration. Typical bursts range from about 10 μs to about 1 ms in duration. If data are lost or corrupted during transmission, bursts are retransmitted until they are successfully received. Also, under conditions where communications are poor, e.g. due to weak signal strength, the systems can lower their data-transfer rates to have better signal-to-noise ratios and improved reliability. This increases the cumulative time that it takes to transmit a given

amount of data. Thus, high signal strengths from Wi-Fi devices (during transmission of bursts) do not necessarily translate to higher exposures, because this results in lower duty factors (Mann, 2010).

Comprehensive data are yet to be published regarding the duty factors of Wi-Fi equipment during normal use; however, Khalid *et al.* (2011) has reported initial results from the use of data-traffic capturing and packet-counting equipment in school networks. Transmitted bursts were captured to determine the proportion of time during which Wi-Fi devices transmitted while children were using laptops during their lessons. The laptops were mostly used for receiving traffic from the access points and therefore laptop-transmit times were low. Duty factors for the monitored laptops were consistently less than 1% and those of access points were less than 10%. Baseline duty factors of access points (with no data being transferred) are about 1%, due to beacon pulses of duration 1 ms that are produced at a rate of ten pulses per second (Mann, 2010).

The SAR values produced when using laptop computers equipped with Wi-Fi transmitters have been evaluated by several authors. Most devices now have built-in antennae located around and along the top edge of the screen, which are therefore at greater distances from the body than a mobile phone held against the head. The rapid reduction in field strength that occurs with increasing distance means that SARs can be expected to be much lower than from mobile phones under such scenarios. Based on a continuous radiated power of 100 mW under a range of such scenarios, Findlay & Dimbylow (2010) calculated a maximum 10 g averaged SAR of 5.7 mW/kg in the head.

When Wi-Fi devices are able to transmit continuously with their antennae in close proximity to the body, the SARs may be higher than in the scenario described above. For example, Kühn *et al.* (2007a) measured a SAR of 0.81 W/kg in a flat phantom with the antennae of a Wi-Fi access point in close proximity and Schmid *et al.* (2007b) measured a SAR of 0.05 W/kg under similar conditions from a Wi-Fi equipped PCI card inserted into a laptop. The value reported by Kühn *et al.* is within the range of maximum localized SARs from mobile phones (ICNIRP, 1998).

Studies have also examined the general field strengths in environments where Wi-Fi networks are installed. Foster (2007) measured RF fields at 55 public and private sites in the USA and Europe (4 countries), which included private residences, commercial spaces, and health-care and educational institutions. In nearly all cases, the measured Wi-Fi signal levels were far lower than other RF signals in the same environment. The maximum time-averaged power density in the 2.4-GHz band measured at 1 m distance from a laptop uploading and downloading a file was 7 mW/m^2, which is far less than the ICNIRP (1998) reference level value of 10 W/m^2 for the general public.

Schmid *et al.* (2007a) investigated the typical exposure caused by wireless local area network (WLAN) applications in small and large indoor public areas (e.g. Internet cafés, airports). Outdoor scenarios were also considered where the exposure was measured in the vicinity of access points serving residential areas and public places. Exposure was assessed by computational methods and by on-site measurements. The highest values for indoor exposure were found close to the transmitting devices (access points or clients) where, at a distance of about 20 cm, spatial and temporal peak values of power density were found to reach about 100–200 mW/m^2. In general, the exposure values were several orders of magnitude below the ICNIRP (1998) reference levels.

(d) Industrial applications

There are several industrial applications for RF-EMF, many of which are described in review reports and papers. On the whole, the

literature is rather old and difficult to interpret since reported field values have generally been taken in the context of compliance assessments rather than epidemiological studies, so it is hard to judge what the typical exposures of workers may have been. Only a brief description of some of the sources producing the highest exposures is included here.

(i) Industrial induction heating

Industrial induction heating involves the use of induction furnaces equipped with large coils that produce strong magnetic fields. Conducting materials for treatment are placed inside the coils and the magnetic fields cause eddy currents, resulting in heating of the conducting materials. Typical applications include surface hardening, softening and melting metals, mixing alloys and heating gaseous conductors such as plasmas. The frequencies used span a wide range, from 50 Hz through to a few megahertz, so not all applications fall within the scope of this *Monograph*. The fields can be considerable and worker exposures are greatest for tasks that involve approaching the coils, e.g. when taking samples from within the coils of open furnaces. The coil impedances increase with frequency and electric fields can become the dominant contributor to exposure (rather than magnetic fields) at frequencies above about 100 kHz (ICNIRP, 2009a). Allen *et al.* (1994) have provided a review of measured exposures, drawing on peer-reviewed papers from several countries and measurements made in the United Kingdom.

(ii) Dielectric heating

RF heating and drying equipment has been used for many years and applications include preheating, wood-glueing and polyvinyl chloride (PVC) welding. These materials are lossy dielectrics and their conductivity at radiofrequencies means that they can become heated-up when placed in a strong electric field. Typical heaters are designed to use the industrial, scientific and medical (ISM) bands at 13.56, 27.12 and 40.68 MHz, but reported measurements show that frequencies are variable within the range 10–80 MHz. Powers range from less than a kilowatt to tens of kilowatts for typical heat sealers, while for glue-dryers the maximum power may exceed 100 kW (ICNIRP, 2009a).

The greatest source of operator exposure comes from the use of manually actuated PVC dielectric machines, where the operator manipulates material to be welded by hand and then clamps it between a pair of electrodes between which the power is applied. Measurements and other details from studies carried out in the United Kingdom and elsewhere are described by Allen *et al.* (1994). The field strengths from dielectric heaters at the operator locations can be in excess of the ICNIRP (1998) reference levels, but they are non-uniform and it is necessary to evaluate the SAR in the body to determine compliance with the guidelines. Kännälä *et al.* (2008) have developed an assessment method based on measuring induced limb currents and relating these to localized and whole-body SARs (wbSARs).

(e) Medical applications

RF fields have several medical applications. In general, exposure for the clinician will be lower than for the patient, since the RF source will generally be located closer to the patient, but this is not always the case. RF fields can also be applied for therapeutic purposes, for moderate heating of tissue, or for much greater heating for the cutting and destruction of tissue during surgery.

(i) Magnetic resonance imaging (MRI)

Performing an MRI scan for diagnostic purposes involves strong RF fields. MRI uses a combination of EMFs to produce exceptionally clear images of tissue structures inside the human body, to assist with medical diagnoses. Hydrogen atoms associated with water in the

body tissues are made to resonate in a strong magnetic field such that they emit RF radiation at the resonant frequency. Therefore, variations in the water content of tissues are the basis of the contrast in the images obtained (HPA, 2008).

A permanent uniform static magnetic field, typically in the range 1–3 T, but sometimes up to 8 T or more with specialized systems, is applied over the body and causes splitting of the energy states associated with protons (hydrogen atoms). The difference between the energy states is such that protons will transfer from the lower to the upper energy state in response to an applied RF signal at the resonant frequency. Protons will also fall back to the lower energy state spontaneously, and in doing so emit RF radiation at the Larmor frequency. The Larmor frequency is given by 42.57 times the static magnetic-field strength. Thus a 1.5 T, an MRI scan involves the application and measurement of RF fields at 64 MHz (HPA, 2008).

During an MRI scan, multiple RF pulses (hundreds to thousands per second) are applied over either the whole body or the part of the body being visualized. The RF dose (SAR) received by patients inside the MRI scanners is reported by the system and can vary from < 0.1 W/kg to about 4 W/kg for more complex settings (HPA, 2008). The desire to limit temperature increases and prevent harm to the patient can be a limiting factor in how quickly scans can be performed in practice. Clinicians and any other personnel who are near to the magnet during the scans will be exposed to the RF fields, but the strength of the RF fields will diminish rapidly with increasing distance from the RF coils and the space between them inside the scanner.

(ii) Diathermy

Short-wave and microwave diathermy are used to gently warm muscles, tendons and joints to alleviate a variety of medical conditions. Short-wave equipment operates at frequencies of 13.56 MHz or 27.12 MHz and powers of about 400 W. Applicators for microwave diathermy operate at 2.45 GHz with powers of about 200 W and tend to take the form of a radiating antenna surrounded by reflectors that direct the emitted energy in a forward direction. While exposure of the patient is intentional, the scanner operators close to the equipment may be exposed involuntarily in areas where field strengths are high, unless they move away while the equipment is in operation (ICNIRP, 2009a).

(iii) Surgical diathermy and ablation by radiofrequency

RF fields and currents are widely used during surgical procedures. In surgical diathermy or electrosurgery, a small hand-held electrode acts as a cutting or coagulation instrument. The basic operating frequency is typically about 500 kHz and there are harmonics produced at frequencies up to around 20 MHz. Current densities in tissues can be as high as 10 A/cm^2 with source powers of up to 200 W (IPEM, 2010). Some more recent systems use a frequency of 9.2 GHz and powers of about 20 W delivered through needle-like electrodes containing coaxial lines. These systems are employed for minimally invasive surgery, e.g. focal tumour ablation and the treatment of menorrhagia by endometrial ablation (IPEM, 2010).

(f) Domestic sources

There are few powerful sources of RF in the home; however, among these, induction cooking hobs and microwave ovens are of note. Less powerful sources include remote-controlled toys, baby monitors, and the mobile/cordless phones and the Wi-Fi systems described earlier.

Induction cooking hobs feature coils that produce a magnetic field beneath the metal cooking pans that are placed on them. The magnetic fields produce eddy currents in the pans, which are thereby heated. The powers transferred to the pans can be several kilowatts and the frequencies involved are in the range

20–50 kHz. Magnetic fields can be in the order of the ICNIRP reference levels, but vary greatly with user position and also depend on the placement of the pan. ICNIRP (2009a) reviews studies that have investigated these exposures.

Microwave ovens are standard fixtures in many homes and contain microwave sources operating at a frequency of 2.45 GHz and producing powers beteen 500 W and 2 kW. The design of such ovens is such that leakage is kept to a minimum and a product-performance technical standard requires that microwave-power density levels fall below 50 W/m^2 at a distance of 5 cm. Several large surveys of leakage levels have been performed, as described in ICNIRP (2009a), and these indicate that approximately 99% of ovens comply with the emission limit. According to the measurements of Bangay & Zombolas (2003), the maximum local SAR values at the emission limit are 0.256 W/kg and the maximum 10 g averaged SAR is 0.0056 W/kg.

A new source of RF that is currently being introduced and that seems set to enter many homes is the transmitter associated with "smart" metering of electricity consumption and potentially metering for other services such as water and gas. There is no global approach to gathering information from smart meters and relaying it back to the utility companies, but it is clear that radio communications will be involved. Some systems may use mobile-phone networks for this purpose, while others may use dedicated radio infrastructures. Some systems may also involve a home area network (HAN) within which individual electrical devices in the home can relay information about usage to a central collection point, allowing residents to examine the information and make decisions about their energy consumption. Two recent investigations commissioned by the Electric Power Research Institute (available on the EPRI webpage) suggest that the power level of radio transmissions will be similar to that of mobile phones, but that the duty factors will be low (on average, such devices will transmit for a small proportion of time only). Low duty factors, combined with the greater distances of these devices from people compared with mobile phones, imply that exposures will be low when compared with exposure guidelines.

(g) Security and safety applications, including radar and navigation

A variety of systems used for security purposes invole the application of RF, including systems for asset tracking and identification. These sources and exposures have been reviewed in ICNIRP (2009a).

Radar systems operate across a broad range of frequencies, mostly in the range 1–10 GHz, with some short-range applications in the range of tens of gigahertz. Emissions from these systems represent an extreme form of pulse modulation, the TDMA scheme used by some mobile phones being a less extreme example. The duty factor in a GSM TDMA signal is 1/8, whereas it is typically around 1/1000 with a radar signal. The typical duration of a pulse might be about a microsecond, while a typical pulse period might be about a millisecond, although these parameters do vary and depend on the type of radar involved. Very high power densities can be produced in the antenna beams during the pulses, and powers can still be high after duty factors are taken into account to determine the average power. To assess human exposure from radar systems it is necessary to take into account:

- The exposure metric of interest (to account for the pulsing, or simply based on the average power);
- People's juxtaposition to the beams (are the beams going over people's heads?);
- The duty factor associated with the pulsing;
- The duty factor associated with rotation (equal to the beam width in azimuth divided by 60 degrees; probably around 200 : 1 in the direction that a rotating beam sweeps through).

Information about radar systems can be found in the following review reports: Allen *et al.* (1994), Cooper (2002) and ICNIRP (2009a).

(i) Air traffic control

The most familiar application of radar is for navigation and the tracking of aircraft movements from rotating ground-based antennae, e.g. at airports. Long-range systems operate over 1–2 GHz, while moderate-range systems operate over 2–4 GHz. The antennae tend to be mounted sufficiently high that buildings cannot obstruct their view of the sky and they form narrow beams of about a degree in the horizontal plane that sweep around 360 degrees once every few seconds. Beams are broader in the vertical plane and tail off in strength towards low elevation angles to avoid reflections from objects on the ground. Aviation radar systems have quite high emitted power levels during the pulses, typically from tens of kilowatts to a few megawatts. Taking the duty factors into account leads to time-averaged emitted powers of about 100 W to a few kilowatts (AGNIR, 2003).

(ii) Marine radar

Marine radar systems are used to inform the crew of a ship of the presence of other vessels and thus avoid collisions. The range of these systems is shorter than that of aviation systems. It is known that targets will be at ground (sea) level, so the beam profile extends to ground level in the plane of elevation. The rotating antennae are mounted at height to allow a view of the sea that is unobstructed by the structure of the ship/vessel on which they are carried. Operating frequencies are in the ranges of 2–4 or 8–12 GHz. Mean powers are in the range 1–25 W and peak powers can be up to about 30 kW (ICNIRP, 2009a).

(iii) Tracking radar

Tracking radar is used in military systems to lock-on to and follow targets such as aircraft and missiles. The antennae can rotate, execute a nodding motion, point in a fixed direction, or follow a target. Targets are not expected to assist with being tracked and may even be designed with stealth in mind and to suppress the extent to which they reflect radar pulses. Hence, tracking radar systems generally involve higher powers than navigation systems and use peak powers of up to several megawatts. Systems mostly operate between 2 and 8 GHz. Certain tracking radar systems can produce mean power densities > 100 W/m^2 at distances in excess of a kilometre, even after duty-cycle correction (ICNIRP, 2009a).

(iv) Whole-body security scanners

Whole-body security scanners are used in places such as airports to generate images of objects carried under people's clothing without the need for physical contact. Active systems transmit either ionizing (X-rays) or non-ionizing (RF) radiation towards the body and then analyse the scattered radiation. Passive systems simply monitor the "black body" (thermal) radiation given off by the body in the RF spectrum and do not emit any radiation. Current active RF systems typically operate at about 30 GHz, although in the future systems may use frequencies of up to several hundred gigahertz. (European Commission, 2010). A note published by AFSSET (2010) described an assessment of an active scanner operating in the frequency range 24–30 GHz. Power densities incident on the body were reported as between 60 and 640 μW/m^2.

(v) Other systems

Various other radar systems include those used for monitoring weather, traffic speed, collision avoidance with vehicles and ground penetration.

1.3 Dosimetry

1.3.1 Introduction

Incident EMFs are defined as external fields in the absence of – i.e. without interaction with – the human body, animals, or tissue samples. Incident fields couple with the human body and induce EMFs and currents inside the body tissues.

Macrodosimetry is the science of quantifying the three-dimensional distribution of EMFs inside tissues and organs of biological bodies, with averaged induced fields across submillimetre tissue structures (e.g. cells). The term is also applied to measurements in media that have dielectric characteristics similar to those of biological bodies, e.g. cell cultures, tissue-simulating media, etc. The induced fields are the only exposure parameters that can interact with biological processes and, therefore, provide the primary exposure metric (Kühn, 2009).

Microdosimetry refers to the assessment of fields at subcellular resolution (e.g. across membranes, proteins, etc.). This is a relatively new research area that faces various basic problems, such as material models and transitions between classical and quantum electrodynamics. In all cases, however, macrodosimetry is the first step, since microdosimetry can only be developed from the locally averaged induced fields. This *Monograph* does not cover microdosimetry, and "dosimetry" used hereafter thus refers to macrodosimetry. Dosimetry studies of differences in dielectric properties of tissues in human and animals models published since 1984 are described in Table 1.7.

The coupling mechanisms of the electric and magnetic incident-field components are different. Hence, both must be determined separately to fully characterize human exposure. Since coupling with the human body also depends on the ratio of wavelength versus body size, the RF-EMF spectrum is often divided into at least three ranges, e.g. 30 kHz–10 MHz (below body resonance); 10 MHz to 2 GHz (body and partial body resonances); and 2 GHz to 300 GHz (surface-dominated absorption) (ICNIRP, 2009a). Furthermore, the distribution of the induced field strongly depends on various parameters, such as source (strength, frequency, polarization, direction of incidence, size, shape, etc.), distance and location of the source with respect to the body, outer anatomy, inner anatomy, body posture, and environment of the body (e.g. reflective objects).

The field variations within the body are generally large and may well exceed a factor of thousand for the locally absorbed energy. In general, field distributions change considerably between different postures and orientations of the body with respect to the field. For example, the exposure of the brain may change even though the whole-body average and the peak spatial absorption remain the same.

1.3.2 Dosimetric exposure

It has only recently become technically possible to achieve a detailed characterization of exposure to EMFs. Hence, research on dosimetry during the past 30 years has been focused on reliable determination of the exposure metric as defined in the safety guidelines, namely, the maximum average whole-body values and the maximum locally-induced field values. The most commonly used metrics are defined below.

At frequencies greater than 100 kHz, SAR is the main measure of exposure used. SAR is the absorbed electromagnetic energy per tissue mass and can be calculated directly from the electric energy loss, which is proportional to the square of the locally induced root-mean-square value (rms) of the electric field strength, the induced current density and the temperature increase (see Glossary for detailed equations). The assessment on the basis of the initial rise in temperature is only valid if the exposed body is in thermal

Table 1.7 Dosimetry studies of differences in dielectric properties of tissues

Reference	Description of the model	Main results and comments
Thurai *et al.* (1984)	Variation of dielectric properties of brain tissue of the mouse	Measurements were made on the cerebral cortex at frequencies of 10 MHz to5 GHz in six groups of mice aged 3, 5, 19, 26, 33 or 58 days. Values of relative permittivity and conductivity are shown.
Thurai *et al.* (1985)	Dielectric properties of the developing rabbit brain	The dielectric properties of developing rabbit brain were measured at 37 °C, at frequencies between 10 MHz and 18 GHz, with time-domain and frequency-domain systems. Water dispersion in the brain becomes more complex with age.
Kuster & Balzano (1992)	Mechanism of energy absorption by biological bodies in the near field	Heterogeneous tissues and larger biological bodies of arbitrary shape are generalized for frequencies above 300 MHz. The SAR is found to be mainly proportional to the square of the incident H-field, which implies that in the close near field, the psSAR is related to the antenna current and not to the input power.
Lu *et al.* (1994)	Dielectric properties of human erythrocytes at radiofrequency	Dielectric properties of human erythrocytes in suspension (haematocrit, 50%) from 243 healthy persons (120 men, 123 women) were measured at 25 °C, at frequencies of 1–500 MHz, with a coaxial transmission line-reflection method (one-side measurement). A statistically significant age-dependence was found, with a critical age of about 50 yr, above which permittivity and conductivity of human erythrocytes in suspension decreased significantly.
Peyman *et al.* (2001)	Variation of dielectric properties of rat tissues by age, at microwave frequencies	The dielectric properties of tissues from rats of six different age-groups were measured at 37 °C in the frequency range 130 MHz to 10 GHz, with an open-ended coaxial probe. The percentage decrease in the dielectric properties of certain tissues in rats aged 30–70 days rats at mobile-phone frequencies was tabulated. These data contribute to rigorous dosimetry in lifetime-exposure animal experiments, and provide insight into possible differences in assessment of exposure for children and adults.
Peyman & Gabriel (2002)	Variation of dielectric properties of biological tissue, by age	Dielectric properties of the bone marrow generally decrease with age, due to changes in water content.
Jaspard *et al.* (2003)	Dielectric properties of blood, by haematocrit value	Two dielectric parameters appeared to be strongly dependent on the haematocrit value. The permittivity *vs* frequency decreases then increases when the haematocrit decreases. The conductivity increases in the whole frequency range when the haematocrit decreases.
Schmid *et al.* (2003)	Pre- and post-mortem dielectric properties of porcine brain tissue	Conductivity declined 15% (at 900 MHz) and 11% (at 1800 MHz) within 1 h after death, The decline in permittivity was 3–4%, and almost frequency-independent. In-vitro measurements of dielectric properties of brain tissue underestimate conductivity and permittivity of living tissue. These findings may affect generally accepted data on dielectric properties of brain tissue widely used in RF dosimetry.
Gabriel (2005)	Variation of dielectric properties of rat tissues, by age	Age-related dielectric data for 9 of 34 rat tissues were incorporated in a numerical dosimetry study on anatomically heterogeneous animals with body sizes corresponding to the ages of 10, 30, and 70 days, exposed to plane waves at spot frequencies from 27 to 2000 MHz. The variation in the dielectric properties affect the wbSAR by < 5%; the most conservative value (highest SAR) is obtained when 70-days properties are used. The dielectric properties of whole brain, skin, and skull were determined experimentally in the frequency range 300 KHz to 300 MHz.

Table 1.7 (continued)

Reference	Description of the model	Main results and comments
Lee *et al.* (2006)	Development of a body model for the Korean adult male	The dimensions of the human body vary by age, sex, and race. The internal structure and outer dimensions of a body exposed to an electromagnetic field are important for accurate dosimetry. Two volunteers with body dimensions representative of the average Korean adult male were recruited and scanned for phantom development by use of magnetic resonance and computed tomography. About 30 different tissues were manually classified by an anatomist on the raw images. The whole-body phantom can be used for radiation protection dosimetry.
Christ *et al.* (2006)	Electromagnetic near-field absorption in layered biological tissue in the frequency range 30–6000 MHz	The increase in SAR depends mainly on the thickness of the fat tissue and the frequency. For frequencies between 236 MHz and 5.8GHz, the peak spatial average SAR can increase by a factor between 1.6 and 3.5 compared with homogeneous tissue-simulating liquid. In the near-field zone, reactive E-field components give rise to increased peak spatial averaged SAR, due to high absorption in the skin
Peyman & Gabriel (2007)	Development and characterization of tissue-equivalent liquids	Dielectric properties of two tissue-equivalent liquids were measured in the frequency range 30–3000 MHz. A sucrose-based solution had a permittivity of 61.3 ± 1.0 and a conductivity of 0.63 ± 0.02 S/m at 30 MHz. An aqueous diacetine solution had a permittivity of 54.2 ± 1.2 and a conductivity of 0.75 ± 0.01 S/ m at 30 MHz. At 150 and 300 MHz, the two liquids met the specified target to within 5% and 10%, respectively.
Peyman *et al.* (2007)	Dielectric properties of porcine cerebrospinal tissues *in vivo*, *in vitro*, and by systematic variation of age	Dielectric properties of pig cerebrospinal tissue were measured *in vivo* and *in vitro*, in the frequency range of 50 MHz to 20 GHz. The study *in vivo* included tissues from pigs of different ages, weighing about 10, 50 and 250 kg. Dielectric properties of white matter and spinal chord, but not grey matter, showed significant variation with age.
Lee *et al.* (2009)	Development of a body model for a Korean child aged 7 yr	A whole-body voxel model of a 7-yr-old male volunteer was developed from 384 axial MRIs. The model was adjusted to the physical average of Korean boys aged 7 yr. The body weight of the adjusted model, calculated with the mass-tissue densities, is within 6% of the 50th percentile weight.
Peyman *et al.* (2009)	Dielectric properties of tissues and SAR in children exposed to walkie-talkie devices	Dielectric properties of porcine tissues *in vitro* – measured from 50 MHz to 20 GHz – show significant reduction with age. Both permittivity and conductivity decreased in 10 out of 15 tissues measured, mainly due to reduction in the water content of tissues in the ageing animal. The results were then used to calculate the SAR values in children aged 3–7 yr exposed to RF induced by walkie-talkie devices. No significant differences between the SAR values for the children of either age or for adults were observed.

MRI, magnetic resonance imaging; RF, radiofrequency; SAR, specific absorption rate; wk, week or weeks; yr, year or years

equilibrium or in a steady thermal state at the beginning of the exposure.

The SARs usually reported are values averaged over time, either over the periodicity of the signal or over any period of 6 minutes. Two metrics are most often determined:

- The whole-body-averaged SAR (wbSAR) is the total electromagnetic power absorbed by a body divided by its mass.
- The maximum peak spatial SAR (psSAR) averaged over any cube inside the body with a tissue mass of 1 g (psSAR-1 g) or 10 g (psSAR-10 g). Specific evaluation rules have been defined in which the cube is grown around the observation point, whereas special rules apply in case of air interfaces (see ANSI/IEEE, 2002a). This value is usually reported independently of the exposed tissue.

In recent years, the focus has shifted towards more tissue-specific measures of exposure that can be correlated with biological effects (Kuster *et al.*, 2006; Boutry *et al.*, 2008). Examples are:

- Instant, time-averaged or cumulative organ- and tissue-specific SAR;
- Distributions and histograms of the spatially averaged SAR (sSAR) values over a mass of 1 g or 10 g of tissue in the shape of a cube (sSAR-1 g or sSAR-10 g) or 10 g of contiguous tissue (sSAR-10 g c) (see also Ebert, 2009).

At frequencies below 10 MHz, the following quantities are used:

- Current density averaged over any 1 cm^2 of tissue from the central nervous system (CNS) perpendicular to the current direction (ICNIRP, 1998);
- Electric field integrated over any line segment of 5 mm in length oriented in any direction within the tissue (IEEE, 2005);
- Electric field averaged in any $2 \times 2 \times 2$ mm^3 volume (ICNIRP, 2010).

1.3.3 Coupling of incident fields with the body

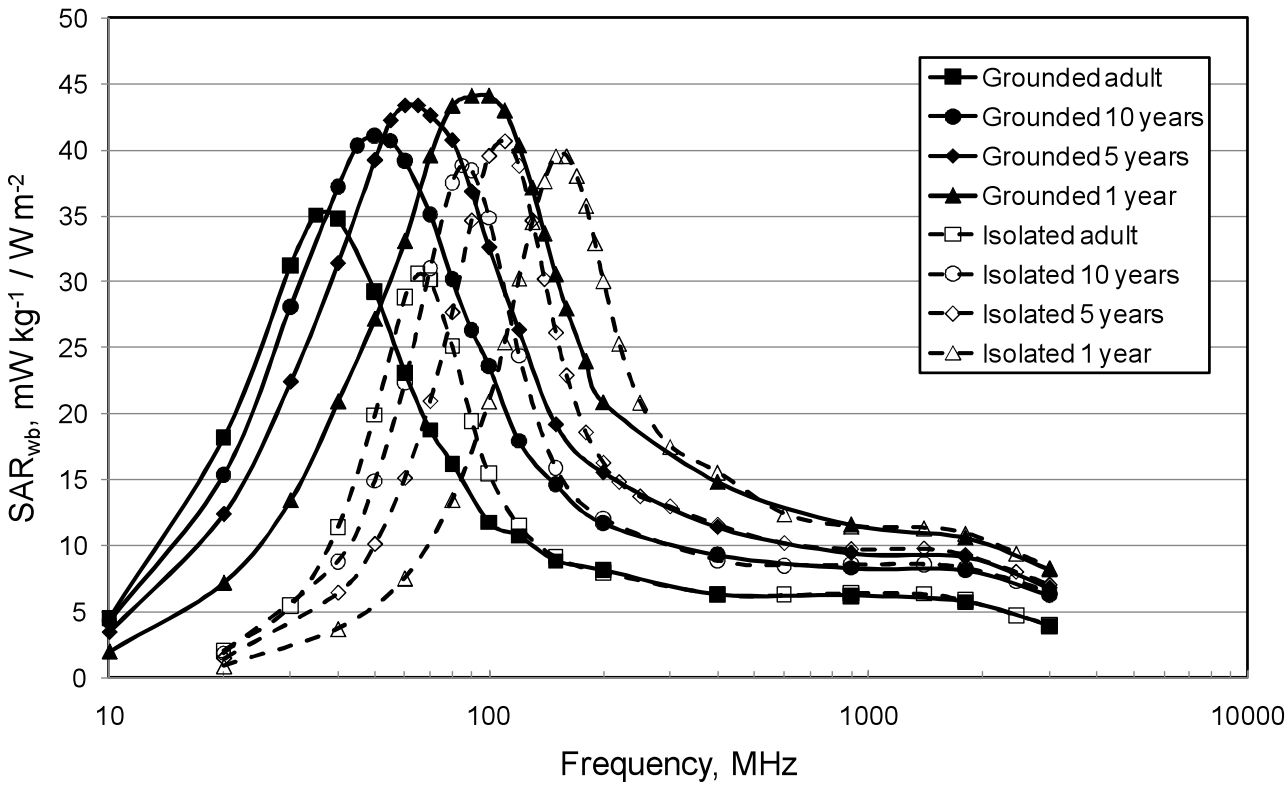
(a) Body-mounted devices

For transmitters operating at frequencies greater than 300 MHz, the absorption in proximate human tissue is approximately proportional to the square of the incident magnetic field (H_{inc}) at the skin surface of the person exposed (Kuster & Balzano, 1992). H_{inc} is approximately given by the square of the equivalent RF current in the device (I_{RF}) divided by its distance from the human body (d).

The equations presented by these authors explain many aspects of human exposure to radiation from mobile phones discussed in this *Monograph*, namely:

- Mobile phones close to the body ($d < 0.01$ m) are the dominant source of exposure, particularly of the brain, when the phone is held at the ear, compared with exposure from the more powerful base stations at larger distances ($d > 10$ m).
- Exposure from a mobile phone operated by a bystander ($d < 1$ m) may still exceed the exposure from a base station at moderate distance.
- The absorption of energy by different tissues is strongly dependent on the design of the phone, and may vary more than 20-fold according to, e.g. the location of the antenna, and the current distribution with respect to the tissue (Kuster *et al.*, 2004).
- The level of local exposure is also relatively strongly dependent on the position of the phone at the head, and may vary by a factor of more than 10 (Wiart *et al.*, 2007; Gosselin *et al.*, 2011).
- The exposure of children is higher than that of adults by a factor of approximately two due to the different shape of children's heads, which brings the phone geometrically closer to the brain in children

Fig. 1.12 Variation in the whole-body specific absorption rate (SAR) produced per unit power density as a function of frequency in the adult male phantom NORMAN, and child phantoms of three different ages, standing on a conductive floor (grounded) and insulated



than in adults (see Section 1.6.1 (ii); Wiart *et al.*, 2008).

- Hand-free kits reduce the psSAR in head tissue by a factor of 100 and more (Porter *et al.*, 2005; Kühn *et al.*, 2009b; also see Section 1.2.2).
- Bluetooth headsets operate at 1 mW and the maximum psSAR is a factor of about 100 lower than that for a mobile phone operating at the ear (Kühn *et al.*, 2007a).
- WLAN transmitters in a laptop computer also result in lower exposures to the brain than a mobile phone operated at the ear.
- Exposures from DECT base-station antennae located in the same room as the person are similar to those from mobile-phone base stations in the neighbourhood (Kühn *et al.*, 2007a).

(b) Whole-body and partial-body resonances

The human body can be described as an elongated poor conductor. Therefore, it couples energy best if the electric field is polarized along the long body axis and when the electrical length of the body is resonant, i.e. approximately half a wavelength (λ/2) for an ungrounded body and one quarter wavelength (λ/4) for a person standing on a grounded floor. This was first investigated with ellipsoids and recently refined with newly available human models (e.g. Dimbylow, 2007a; Conil *et al.*, 2008; Kühn *et al.*, 2009b). The typical variation in wbSAR as a function of frequency is shown in Fig. 1.12. The same effects have been investigated for partial-body resonances (Kühn *et al.*, 2009b). The results of these modelling studies explain the main characteristics

Table 1.8 Depth of penetration of muscle and fat by radiofrequency fields at typical telecommunication frequencies

Frequency (MHz)	Muscle			Fat		
	Relative permittivity	Conductivity (S/m)	Penetration depth (mm)	Relative permittivity	Conductivity (S/m)	Penetration depth[a] (mm)
400	57.13	0.80	52	5.58	0.041	310
900	55.03	0.94	42	5.46	0.051	244
1800	53.55	1.34	29	5.35	0.078	158
2450	52.73	1.74	22	5.28	0.105	116
5200	49.28	4.27	8.8	5.01	0.255	47

[a] Penetration depths have been calculated based on the equation given in the Glossary.
MHz, megahertz; mm, millimetre; S/m, siemens per metre
Compiled by the Working Group from *Tissue Properties Database: Dielectric Properties* by IT'IS Foundation: http://www.itis.ethz.ch/itis-for-health/tissue-properties/database/dielectric-properties/

of far-field exposures of between 10 MHz and 2 GHz, i.e. a strong dependence on body size and posture, and on polarization.

(c) *Below whole-body and partial-body resonances*

At exposures below the body-resonance frequency, i.e. < 10 MHz, the body can be described as a short poor conductor. The dominant exposures of concern are from near-field sources that generally have strong field gradients. Under these conditions, the energy is capacitively coupled in the case of a dominant electric-field source (dielectric heaters, diathermy applicators, etc.) or inductively coupled in the case of a dominant magnetic-field source (e.g. inductive cooking hobs, anti-theft systems, wireless power transfer systems, MRI, etc.). Strong induced currents are also caused by touching metallic objects such as fences or towers exposed to fields from transmitting antennae (contact currents).

(d) *Above whole-body and partial-body resonances*

At exposures above the body-resonance frequency, i.e. > 2 GHz, the body can be described as a dielectric object that is large with respect to the wavelength and the penetration depth (see Table 1.8). Therefore, the absorption is approximately proportional to the exposed surface area of the body (Gosselin *et al.*, 2011). In this case, the wbSAR is proportional to the largest ratio of body surface and weight (Kühn, 2009), whereas the RF energy is predominantly absorbed at the body surface.

1.3.4 Dependence on local anatomy

(a) General

Local exposure is altered by local anatomy due to inhomogeneity of the body tissues. In particular, local enhancements or hot spots can be expected as a result of impedance matching on layered structures, e.g. skin–fat–muscle layers (Christ *et al.*, 2006), and due to narrowing cross-sections of highly conductive tissues. An example of the latter is high exposure in the ankles when the body is grounded and the electric-field frequency is in the range of or below body resonance; the ankle consists mostly of low-conductive cartilage and the integrated current is largest close to the feet of the grounded person (Dimbylow, 2005).

(b) Mobile phones

During the last decade, the dosimetric analysis of exposure to radiation from mobile phones has focused on reliable compliance testing of the phones with respect to the limits defined

for psSAR-1 g and psSAR-10 g. The absorption values for different mobile phones are determined in homogeneous head phantoms, i.e. the specific anthropometric mannequin (SAM) in touch and tilted positions. The SAR values for different phone positions have been compared in various anatomical models of the head of adults and children. Reviews of these studies concluded that the psSAR assessed with the SAM is a conservative measure of exposure of both adults and children (Christ & Kuster, 2005; Martens, 2005; Wiart *et al.*, 2005) and that variations in psSAR among different models can be attributed to individual anatomical differences, but not to age-dependent changes in head size (Kainz *et al.*, 2005).

The effects of age-dependent changes in tissue conductivity have been studied by several authors in various rodent species (Thurai *et al.*, 1984, 1985; Peyman *et al.*, 2001; Gabriel, 2005; Schmid & Überbacher, 2005).

Christ *et al.* (2010a) investigated the effect of the anatomical differences on specific tissue exposures in humans. These studies concluded that:

- Exposure of regions inside the brain of young children (e.g. hippocampus, hypothalamus, etc.) can be higher by 1.6–3-fold than that in adults.
- Exposure of the bone marrow in the skull of children can exceed that in adults by a factor of about 10, which is due to the high electric conductivity of this tissue at a young age.
- Exposure of the eyes of children is higher than that of adults. Regarding thermal effects, however, this does not present a problem as exposure to the eyes from mobile phones is very low, i.e. < 10% of the psSAR.
- Because of their different locations relative to the ear, brain regions close to the surface of the skull can exhibit large differences in exposure between adults and children. The cerebellum of children can show a psSAR that is > 2.5-fold that of the local exposure of the cortex of adults. It should be noted that these differences are strongly dependent on the current distribution in the phone, i.e. on the phone design.
- Tissues or anatomical regions that are located at a comparable distance from the phone in adults and children, e.g. the pineal glands, do not show age-dependent variations in exposure.

1.3.5 Estimation of local tissue temperature based on psSAR

In general, the relationship between tissue temperature and psSAR depends strongly upon blood perfusion of the tissue, which varies across the body. In addition, local hot spots (points of elevated temperature) are influenced by thermal conductivity.

The correlation between psSAR and the increase in temperature for exposures to dipoles and mobile phones operated close to the head has been studied (Hirata *et al.*, 2003; Fujimoto *et al.*, 2006; Hirata *et al.*, 2006a, b, 2008). The results of these studies show that the correlation for a given frequency and exposure type is often good, but that the scaling factor strongly depends on the frequency, the spatial averaging scheme and mass, the tissue perfusion, and geometrical aspects such as anatomical surface curvature. The correlation between local averaged SAR and temperature elevation is weak when multiple tissues are involved. In the brain, the relationship between psSAR and peak temperature is found to be poor, and the tissue distribution and the exact exposure situation have a strong impact on brain heating, with thermo-physiological tissue properties particularly affecting the temperature increase in the head for a given psSAR (Samaras *et al.*, 2007; McIntosh & Anderson, 2010).

The temperature increase for multiple anatomical models was estimated over a wide

range of frequencies (0.01–5.6 GHz) for plane waves with different polarization and incident angles. The peak temperature increase for a given psSAR was strongly dependent on anatomy and frequency, with variations of one order of magnitude for the cases investigated (Bakker *et al.*, 2010).

A comparative analysis of seven publications on the increase in brain temperature during mobile-phone use found a high variation (66% at 1800 MHz) in the peak increase in brain temperature relative to the peak averaged SAR in the head (Samaras *et al.*, 2007). These results confirm the finding that the peak temperature increase in the brain should therefore be correlated with peak averaged SAR in the brain and not with the peak averaged SAR in the whole head. Generally, this peak temperature increase in the brain is strongly influenced by absorption in the neighbouring tissues, thus tissue distribution in that anatomical region is important (e.g. the impact of the cerebrospinal fluid) (Hirata *et al.*, 2003).

1.3.6 Dosimetry methods

To demonstrate compliance with safety guidelines, wbSAR and psSAR values are estimated conservatively. In most cases, psSAR values are not correlated with a specific tissue or with typical exposures and, therefore, they can only be used for epidemiological studies when additional assessments and considerations are taken into account.

It is practically impossible to measure EMFs non-invasively or *in vivo*; thus, measurements can only be obtained post mortem. The limitations associated with post-mortem evaluations include: (1) accessibility to certain tissues only; (2) field distortions caused by the invasively introduced probe and dielectric changes due to decreased tissue temperature and blood content; and (3) large uncertainties associated with obtaining accurate measurements near and across tissue boundaries. Only the integrated, total absorbed power can be determined relatively easily by means of the calorimetric method (see Section 1.4.4).

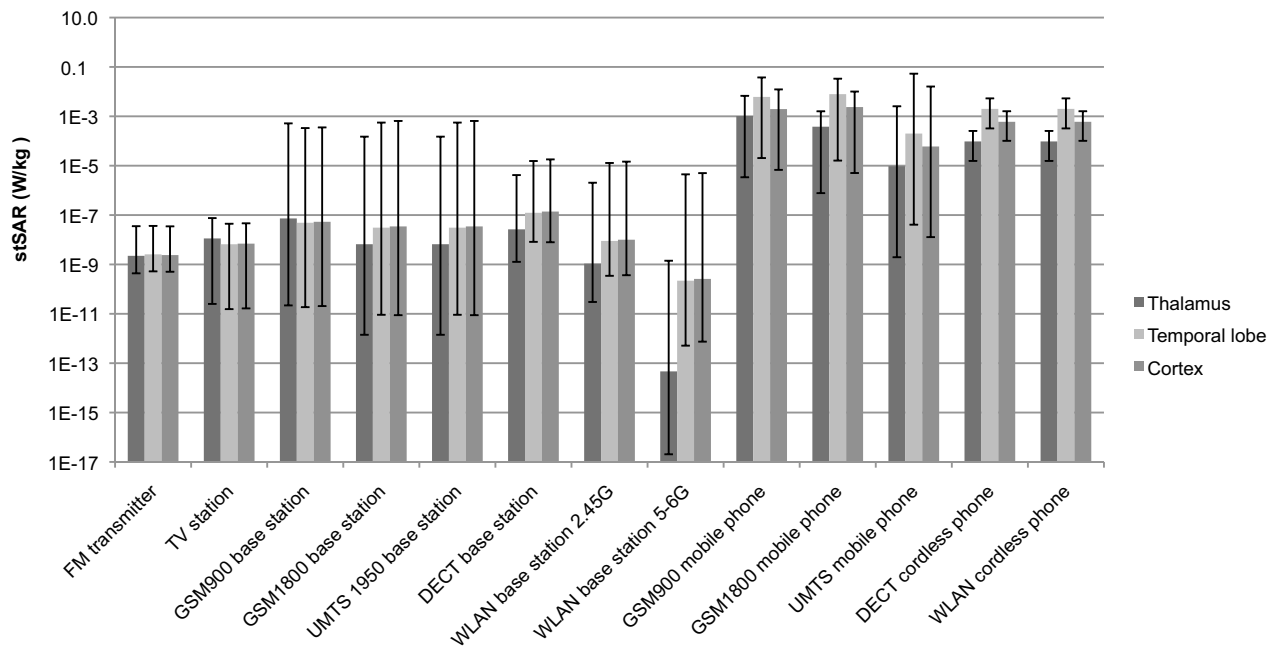
Progress in computational electromagnetics and the exponential growth of computational power and computer memory have facilitated the determination of field distributions in full anatomical models of human bodies with resolutions much smaller than 1 mm^3. The dissipative properties and the low quality-factor of complex anatomical structures pose no special problem for numerical analyses such as the finite-difference time-domain (FDTD) method. A grid resolution of less than 0.2 mm in a specific region of the body and of 0.5–1 mm for uniform resolution is the standard for today's FDTD computations. Finite-element methods (FEM) are also increasingly used, especially for evaluation of exposures below 10 MHz. Approaches such as the combination of the method of moment (MoM) with FDTD, are also regularly applied (Meyer *et al.*, 2003).

Numerical techniques have also become more powerful with the availability of human models that will soon represent the full range of anatomical variation within the human population. Reviews of these models are available (Dimbylow *et al.*, 2009; Christ *et al.*, 2010b; Wu *et al.*, 2011). In some of these models, body posture can be varied. These models are applied to assess typical exposures, to determine interaction mechanisms, and to derive simplified phantoms for compliance testing.

(a) Methods to demonstrate compliance with guidelines

For compliance testing of commercial mobile telecommunication devices that operate very close to the human body, experimental dosimetry is often superior to numerical approaches. The measurement instruments and methods are described in Section 1.4. The sources usually consist of highly resonant components assembled

Fig. 1.13 Estimated tissue-averaged specific absorption rate (stSAR) of the thalamus, temporal lobe and cortex of the brain, induced by various transmission sources



Produced by the Working Group from Kühn *et al.* (2010)

with other electronic and metallic structures. It is difficult to use simulations to predict with certainty if and how secondary resonant structures may be excited, especially in view of the effect of the reflected field of biological bodies on the performance of the device. Small spatial differences can easily result in deviations of more than a factor of two from the actual value. Only when the structure is electromagnetically well defined can a good agreement between simulation and measurement be achieved, i.e. with deviations of less than 20% (Chavannes *et al.*, 2003). It should be noted that detailed information about field distributions inside anatomical bodies is often irrelevant because it cannot be generalized and because differences in anatomy and posture can result in significantly different SAR distributions. However, for safety reasons, the upper boundary (typically the 95th percentile) of the exposure for the entire population is relevant, rather than individual exposure levels. Hence, worst-case phantoms, derived by means of the numerical methods mentioned above, are often applied to assess the upper exposure limits for specific exposure conditions, e.g. during the use of mobile-phone handsets.

(b) Methods to estimate typical exposures

Estimation of typical exposures for specific tissues requires the numerical evaluation of the user's anatomy and usage pattern for the average output power, including its variations. Procedures to make such estimations for different brain regions exposed to mobile-phone radiation have recently been developed (Gosselin *et al.*, 2011). Similar procedures can be applied for other sources. Quantitative estimates are given in Fig. 1.13, which illustrates the estimated tissue-averaged SARs for the thalamus, temporal lobe and cortex when induced by various transmission sources. The typical minimal and maximal values are also given. The basis for these values is shown in Table 1.9. The largest exposure is

Table 1.9 Estimated minimum, maximum and average exposures in the brain from various sources of radiofrequency radiation

Source	Frequency (MHz)	Exposure			
		Average	Minimum	Maximum	Unit
FM transmitter	100	0.02	0.01	0.07	V/m
TV station	700	0.02	0.001	0.05	V/m
GSM900 base station	950	0.05	0.001	4	V/m
GSM1800 base station	1850	0.05	0.001	6	V/m
DECT base station	1890	0.1	0.03	1	V/m
UMTS 1950 base station	2140	0.05	0.001	6	V/m
WLAN base station	2450	0.03	0.007	1	V/m
WLAN base station	5200/5800	0.01	0.001	1	V/m
GSM900 mobile phone	900	50	0.2	250	mW
GSM1800 mobile phone	1750	40	0.1	125	mW
DECT cordless phone	1890	10	3	20	mW
UMTS mobile phone	1950	1	0.0003	200	mW
WLAN cordless phone	2450	10	3	20	mW

Note: Far-field exposures are estimated in terms of incident-field values and exposures from handsets are calculated from time-averaged output power.
Compiled and calculated by the Working Group from Kühn *et al.* (2010)

caused by the GSM mobile telephone, followed by exposures from DECT and WLAN cordless handsets. The new wideband code-division multiple access (WCDMA) systems result in much lower exposure values. It should be noted that the maximum exposure level is very similar for all mobile handsets. The averaged induced fields in the brain resulting from exposure to electromagnetic radiation from base stations of any technology are more than four orders of magnitude lower than those from a handset.

1.3.7 Exposure set-ups for laboratory studies

Properly designed laboratory exposure set-ups with sensitive monitoring systems are critical for producing reliable and reproducible results on the potential health effects of RF radiation. The selection of an exposure set-up is intimately linked to the design and objectives of the study, and includes factors such as the efficiency of the coupling of the incident field with the biological system, the number of animals or cell-culture samples needed per exposure level for statistical analyses, the daily exposure times, and the overall duration of the study. Examples of exposure systems used for this type of study include:

- *Far-field/anechoic chamber*: a room designed to minimize reflections of either sound or electromagnetic waves. To prevent the latter, the inner walls of the chamber are covered with pyramid-shaped RF radiation-absorbent material (Chou & Guy, 1982). Animals or tissue-culture dishes are exposed to RF radiation via an antenna (e.g. horn antenna).
- *Near-field systems*: antennae are used to obtain partial body exposures. In the Carousel system, the animals in restraining tubes are oriented radially around a central antenna at a fixed distance between the nose of the animal and the antenna (Adey *et al.*, 1999). Loop antennae have been used to predominantly expose a particular part of the brain (Lévêque *et al.*, 2004).

- *Transverse electromagnetic (TEM) cell*: an RF-shielded box in which tissue cultures are positioned with a defined orientation relative to the direction of wave propagation and the electric field. A rectangular coaxial transmission line tapered at both ends provides a uniform incident plane wave when RF energy is coupled to the line (Crawford, 1974). Studies with cell cultures and animal models have been conducted in various modified TEM cells (Nikoloski *et al.*, 2005).
- *Waveguide*: a structure that guides and confines electromagnetic waves to propagation in one dimension within a round or rectangular metallic tube. Waveguides have the advantage that only the fundamental mode can propagate within a certain frequency band, correlated with its dimensions. Therefore, resonant systems can be easily used. The power losses of the propagating wave must be carefully evaluated if larger objects are exposed. Standing waves must be appropriately used in case of resonant waveguides or waveguides terminated by a short circuit. Waveguides are widely used for *in-vitro* systems (e.g. Schuderer *et al.*, 2004b). Non-resonant waveguides have also been used to expose rodents (e.g. Guy *et al.*, 1979) and a cascade of 17 sectorial resonant waveguides excited by one quad-loop antenna have been employed to expose one rat per waveguide (Kainz *et al.*, 2006).
- *Radial transmission line (RTL):* a structure that confines the wave to propagate in two dimensions with two parallel metal plates excited between their centres by an antenna. In the case of a non-resonant application, the wave is terminated at the perimeter of the lateral plates with absorbers (Hansen *et al.*, 1999; Moros *et al.*, 1999). The system has been used for studies *in vivo* or *in vitro* by placing the cell cultures or animals at a fixed distance from the antenna. RTL has also been used as a resonant structure in which the wave is terminated with metallic rods instead of absorbers. This configuration has also been called a "Ferris wheel," whereby the animals in restraining tubes are positioned at a fixed distance to the reflecting rods (Balzano *et al.*, 2000). Several improvements have been suggested and implemented (Ebert, 2009).
- *Reverberation chamber*: a shielded room with minimal absorption of electromagnetic energy. To create statistically homogeneous fields inside the chamber when exposure is averaged over time, rotating metallic reflectors (stirrers) constantly create changing boundary conditions. Animals are unrestrained during exposure (Jung *et al.*, 2008).

Regardless of the type of exposure system, for a correct interpretation of the findings and replication of the experiments in other laboratories, it is important that all pertinent electromagnetic-field exposure characteristics (particularly dosimetry) and biological parameters be fully addressed in the experimental design, and properly described in the study reports (Valberg, 1995; Kuster & Schönborn, 2000; Kuster *et al.*, 2006; Belyaev, 2010). These factors are briefly discussed in the next two sections.

1.3.8 Exposure characterization in laboratory studies

The experimental conditions during studies on the effects of exposure to EMF should be described in detail as listed below:

- Signal characteristics should include: carrier frequency, modulation scheme, power level and stability;
- Zone of exposure (near field or far field);

- Polarization (e.g. linear or circular polarization) of the induced EMF with respect to the biological system;
- Performance of the setup: determination of induced electric- and magnetic-field strengths and SAR levels and distribution (numerical dosimetry) in the cell culture, or per organ site in animal experiments; this part should also include an uncertainty analysis;
- Field distribution: should be homogeneous (SD < 30% in cell cultures) and variations in the exposure levels of individual tissues of the exposed animals should be characterized, including details on animal age, movement, posture, weight, etc.;
- The increase in temperature caused by the RF field must be well characterized and reported;
- Control of acoustic noise/vibration level and exposure to ambient RF fields and static fields;
- Monitoring: should include verification of incident field strengths and homogeneity, induced fields, and any changes in the performance of elements of the exposure system over the duration of the experiment, including the long-term reliability of monitoring equipment;
- Experimental design requirements: duration of exposure (hours per day and total number of days), continuous or intermittent (on/off cycles), time of day;
- Inclusion of a sham-exposure group.

1.3.9 *Biological factors in studies in experimental animals*

The biological factors that may affect the study results are briefly described below:

(a) Studies in vivo

- Identification and justification of the selected animal model (species, strain, sex, age at start and end of study, genotype and phenotype, exposure to other agents);
- Animal husbandry: diet (ingredients, nutrient composition and contaminant levels), drinking-water source and treatment, availability or restriction of feed and water during exposures, absence of specific pathogens, caging (cage material, number of animals per cage, bedding material), prevention of exposure to electric currents from water supply, absence/presence of animal restraining devices;
- Environmental controls: temperature, relative humidity, lighting (on/off cycle, intensity), airflow, noise, and background fields;
- Characterization of animal weight, positioning/orientation, movement in the exposure system, and proximity of other animals and cage boundaries during exposure periods.

(b) Studies in vitro

- Composition of the incubation media, including antioxidant levels, free-radical scavengers, presence of magnetic particles;
- Source and/or derivation of the cell system and its characteristics: cell type, species, strain, sex, age, genotype and phenotype;
- Quality of the cell-culture system and its functional condition: cell viability, growth phase and cell-cycling rate, metabolic status, and cell density (which may affect cell–cell interactions);
- Size, shape, and position of the cell-culture vessel;
- Environmental controls, including temperature, oxygen/carbon dioxide levels, air flow.

Table 1.10 Summary of studies on models of partial body exposure

Reference	Description of the model	Main results and comments
Gandhi *et al.* (1999)	EM absorption in the head and neck region	A FDTD method and a new phantom model of the human body at millimetre resolution were used to study EM energy coupled to the head from mobile phones at 835 and 1900 MHz. Homogeneous models are shown to grossly overestimate both the peak 1-voxel and 1-g SARs. It is possible to use truncated one-half or one-third models of the human head with negligible errors in the calculated SAR distributions.
Hombach *et al.* (1996)	EM energy absorption upon modelling of the human head at 900 MHz	Dependence on anatomy and modelling in the human head were investigated for EM energy absorption at 900 MHz from RF sources operating very close to the head. Different head phantoms based on MRI scans of three adults were used with voxel sizes down to 1 mm^3. The phantoms differ greatly in terms of shape, size, and internal anatomy. The results demonstrate that size and shape are of minor importance. The volume-averaged psSAR obtained with the homogeneous phantoms only slightly overestimates that of the worst-case exposure in the inhomogeneous phantoms.
Schönborn *et al.* (1998)	Energy absorption in the head of adults and children	The levels of EM energy absorbed at 835 MHz and 1900 MHz in the heads of mobile-phone users were compared for adults and children. No significant differences between adults and children were found in the absorption of EM radiation in the near field of sources. The same conclusion holds when children are approximated as scaled adults.
Bit-Babik *et al.* (2005)	Estimation of SAR in the head of adults and children	The peak local average SAR over 1 g and 10 g of tissue and the EM energy penetration depths are about the same in all of the head models under the same exposure conditions.
Wang & Fujiwara (2003)	Evaluation of EM absorption in head models of adults and children	Based on statistical data on external shape of the head in Japanese children, two models were developed to assess SAR values in the head of a child exposed to RF radiation. Compared with the local peak SAR in the model of the adult head, there was a considerable increase in the child's head when the output power of the monopole-type antenna was fixed, but no significant difference when the effective current of the dipole-type antenna was fixed.
Anderson (2003)	Peak SAR levels in head models of children and adults	Multipole analysis of a three-layered (scalp/cranium/brain) spherical head model exposed to a nearby 0.4-lambda dipole at 900 MHz was used to assess differences in SAR in the brain of adults and children. Compared with an average adult, the peak SAR-10 g in the brain of children with a mean age of 4, 8, 12 or 16 yr is increased by a factor of 1.31, 1.23, 1.15 and 1.07, respectively. The maximum rise in brain temperature is about 0.14 °C for an average child aged 4 yr, i.e. well within safe levels and normal physiological parameters.
Martínez-Búrdalo *et al.* (2004)	Peak SAR levels in head models of adults and children	The FDTD method was used to assess differences in SAR in the brain of adults and children, at 900 and 1800 MHz. Peak SAR-1 g and peak SAR-10 g all decrease with decreasing head size, but the percentage of energy absorbed in the brain increases.
Fernández *et al.* (2005)	EM absorption in head models of adults and children	The peak SAR in the head model for a child aged 10 yr was 27% higher than that in the phantom of an adult head, when dielectric properties of a child's tissue were applied, based on fitted parameters. For the peak SAR-10 g, an increase of 32.5% was observed.
Keshvari & Lang (2005)	RF energy absorption in the ear and eye of children and adults	The FDTD computational method was used to calculate a set of SARs in the ear and eye region for anatomically correct head models for adults and children. A half-wave dipole was used as an exposure source at 900, 1800 and 2450 MHz. The head models were greatly different in terms of size, external shape and internal anatomy. The SAR difference between adults and children is more likely to be caused by general differences in the head anatomy and geometry of the individuals rather than by age.
Christ & Kuster (2005)	RF energy absorption in the head of adults and children	The conclusions of this review do not support the assumption that energy exposure to children is increased due to smaller size of the head compared with adults, but points at dielectric tissue parameters and the thickness of the pinna (the external part of the ear) as factors that determine RF energy absorption.

Table 1.10 (continued)

Reference	Description of the model	Main results and comments
Hadjem *et al.* (2005a)	SAR induced in models of the head of children and adults	The FDTD computational method was used to calculate SARs for two child-size head models and two adult-size head models, with a dual-band mobile phone. No important difference was observed in the peak SAR-10 g between the two adult models, or between the two child models.
Hadjem *et al.* (2005b)	Ear morphology and SAR induced in a child's head	Using the FDTD method, SARs induced in the heads of children aged 12 yr were calculated for different ear dimensions, at 900 and 1800 MHz. Exposure to the brain was dependent on the morphology of the ear.
Wiart *et al.* (2005)	Modelling of RF exposure in a child's head	Parameters that influence the SAR in children's heads, such as the evolution of head shape and the growth of, e.g. skull thickness, were analysed. The SAR-1 g in specific tissue was assessed in different models of a child's head based on MRI and on non-uniformly down-scaled adult heads. A handset with a patch antenna operating at 900 MHz was used as the exposure source.
Kainz *et al.* (2005)	Dosimetric comparison of SAM to anatomical models of the head	The SAM was used to estimate exposure in anatomically correct head models for head-only tissue. Frequency, phone position and head size influence the calculated SAR-10 g, which in the pinna can be up to 2.1 times greater than the psSAR.
de Salles *et al.* (2006)	Absorption of RF radiation in the head of adults and children	The SAR produced by mobile phones in the head of adults and children was simulated with an FDTD-derived algorithm, with EM parameters fitted to realistic models of the head of a child and an adult. Microstrip or patch antennae and quarter-wavelength monopole antennae were used at 1850 and 850 MHz. Under similar conditions, the SAR-1 g calculated for children is higher than that for adults. In the model of a child aged 10 yr, SAR values > 60% of those for adults are obtained.
Joó *et al.* (2006)	Metal-framed spectacles and implants and SAR in models of the heads of adults and children	The SAR from mobile telephones in the head of adults and children wearing metal-rim spectacles and having metallic implants was calculated by the FDTD method, and compared with the ANSI/IEEE standards and with the EU standard limits for radiation at 900/1800/2100 MHz. A maximum of the SAR in the child's head was found, which in children with metallic implants could be as much as 100% higher than in the adult head. In the case of exposure at 2100 MHz with vertical position of the phone for adults and at 900 MHz for children with metallic implants, the ANSI/IEEE limits were exceeded.
Fujimoto *et al.* (2006)	Temperature increase and peak SAR in head models for children and adults	The correlation between peak SAR and rise in temperature was studied in head models of adults and children exposed to radiation from a dipole antenna. The maximum rise in temperature can be estimated linearly in terms of peak SAR-1 g or peak SAR-10 g of tissue. No clear difference was observed between adults and children in terms of the slopes correlating the maximum rise in temperature with the peak SAR. The effect of electrical and thermal constants of the tissue on this correlation was marginal.
Beard *et al.* (2006)	SAR comparison between SAM phantom and human head models	The SAM was used to calculate the SAR of the pinna, separately from that of the head. In this case, the SAR found in the head was higher than that found with anatomically correct head models. The peak SAR-1 g or SAR-10 g was statistically significantly higher in the larger (adult) head than in the smaller (child) head for all conditions of frequency and position.
Lee *et al.* (2007)	Changes of SAR in head models by age	Four head models, representing different ages, were used to calculate SARs from exposure to three bar-type phones, according to positioning against the ear. Input resistance of the phone antennae in the cheek position increased when head size grew with age, but for the tilt position this value showed a slight decrease. For a fixed input power, the head models by age showed a 15% change in peak SAR-1 g and peak SAR-10 g. For a fixed radiated power, the peak SARs diminished in the smaller head model and were higher in the larger model, compared with those for the fixed input power. A simultaneous change (up to 20–30%) in the conductivity and permittivity of head tissue had no effect on energy absorption.

Table 1.10 (continued)

Reference	Description of the model	Main results and comments
Wiart *et al.* (2007, 2008)	RF exposure assessment in children head	RF exposure in the head tissues of children was analysed with phantom models and with a dipole and a generic handset at 900, 1800, 2100 and 2400 MHz. The SAR-10 g in the head was studied in heterogeneous head models (seven for children, six for adults). The maximum SAR-10 g estimated in the head models of adults and children were small compared with the SDs. However, the maximum SAR-1 g in peripheral brain tissues of the child models (age, 5–8 yr) is about twice that in adult models, which is not seen with head models for children older than 8 yr. The differences can be explained by the lower thicknesses of pinna, skin and skull of the models for the younger child.
Christ *et al.* (2007)	The exposure of the human body to fields from wireless body-mounted or hand-held devices	A generic body model and simulations of anatomical models were used to evaluate the worst-case tissue composition with respect to the absorption of EM energy from wireless body-mounted or hand-held devices. Standing-wave effects and enhanced coupling of reactive near-field components can lead to an increased SAR compared with homogeneous tissue. With respect to compliance testing, the increased SAR may require the introduction of a multiplication factor for the psSAR measured in the liquid-filled phantom to obtain a conservative exposure assessment. The observed tissue heating at the body surface under adiabatic conditions can be significant, whereas the rise in temperature in the inner organs is negligible.
Christ *et al.* (2010b)	RF absorption in the heads of adult and juvenile mobile-phone users	The external ear (pinna) is the spacer between the top of a phone and the head tissue. Variations of this distance as a function of age, the mechanical force on the pinna, and how it affects the psSAR were investigated among adults and children (age, 6–8 yr) while applying a defined force on the ear. The average distances were 10.5 ± 2.0 (SD) mm for children (age, 6–8 yr) and 9.5 ± 2.0 (SD) mm for adults. The pinnae of three anatomical high-resolution head models (one adult, two child) were transformed accordingly. Numerical exposure analysis showed that the reduced distance due to compression of the pinna can increase the maximum psSAR by approximately 2 dB for adults and children, if the exposure maximum is associated with the upper part of the phone.
Lee & Yun (2011)	Comparison of SARs for the SAM phantom and head models for children	SARs in three head models for children (Korean aged 7 yr; European aged 5 or 9yr) were compared with those of the SAM phantom for exposure at 835 and 1900 MHz. Compression of the pinnae, different positions of the earpiece against the ear entrance canal, different skin and fat properties, and different internal fat and muscle morphologies in the tissue near the phone, were analysed. A phone with a monopole antenna was used for the calculation at each frequency. Results show that a compressed pinna did change the SAR values at 835 MHz, but at 1900 MHz there was an average 25–29% increase in SAR-10 g for pinna-excluded and pinna-included tissue. The peak SAR-10 g was very sensitive to subcutaneous fat and muscle structure when touched by the mobile phone; a muscle-dominant internal head structure led to a higher peak SAR-10 g. The SAM phantom does not seem to provide a conservative estimation of exposure of children's heads at 1900 MHz.

ANSI, American National Standards Institute; EM, electromagnetic; EU, European Union; FDTD, finite-difference time-domain; IEEE, Institute of Electrical and Electronic Engineers; MRI, magnetic resonance imaging; psSAR, peak spatial SAR; RF, radiofrequency; SAM, specific anthropomorphic mannequin; SAR, specific absorption rate; SD, standard deviation; yr, year or years

Table 1.11 Summary of studies on models of whole-body exposure

Reference	Description of the model	Main results and comments
Dimbylow (1997)	Calculation of whole-body-averaged SAR in a voxel model	FDTD calculations were made of the whole-body-averaged SAR in an anatomically realistic voxel model of the human body, which consists of approximately 9 million voxels segmented into 37 tissue types. SAR values are presented for an adult phantom and for scaled models of children aged 10, 5 or 1 yr, grounded and isolated in air from 1 MHz to 1 GHz for plane-wave exposure. External electric-field values corresponding to a whole-body-averaged SAR of 0.4 W/kg are also presented.
Tinniswood *et al.* (1998)	Calculation of power deposition in the head and the neck for plane-wave exposures	When the human head becomes a resonant structure at certain frequencies, the power absorbed by the head and neck becomes significantly larger than would normally be expected from its shadow cross-section. Resonant frequencies were 207 MHz and 193 MHz for the isolated and grounded conditions, with absorption cross-sections that are respectively 3.27 and 2.62 times the shadow cross-section.
Hurt *et al.* (2000)	Effects of variation in permittivity on SAR calculations	The authors studied the effect of variation in permittivity values on SAR calculations. Whole-sphere averaged and localized SAR values along the diameter of a 4-cm sphere were calculated for exposures of 1 MHz to 1 GHz. When the sphere is small compared with the wavelength, the whole-sphere averaged SAR is inversely proportional to the permittivity of the material composing the sphere, but the localized SAR values vary greatly depending on the location within the sphere.
Dimbylow (2002)	Calculation of SAR up to 3 GHz	FDTD calculations of whole-body-averaged SAR values were made for frequencies from 100 MHz to 3 GHz at 2-mm resolution without any rescaling to larger cell sizes. The small voxel size allows SAR to be calculated at higher frequencies. In addition, the calculations were extended down to 10 MHz, covering whole-body resonance regions at 4-mm resolution. SAR values were also calculated for scaled versions representing children aged 10, 5 or 1 yr for both grounded and isolated conditions.
Bernardi *et al.* (2003)	SAR and rise in temperature in the far field of RF sources at 10–900 MHz	The EMF inside an anatomical heterogeneous model of the human body exposed at 10–900 MHz was computed with the FDTD method; the corresponding increase in temperature was also evaluated. The thermal model took account of the thermoregulatory system of the human body. Compared with the whole-body averaged SAR, the SAR-10 g shows an increase of 25-fold in the trunk and 50-fold in the limbs, whereas the peak SAR-1 g shows an increase of 30–60-fold in the trunk, and up to 135-fold in the ankles.
Findlay & Dimbylow. (2005)	Effects of posture on SAR	A change in posture can significantly affect the way in which the human body absorbs RF EM radiation. The FDTD method was used to calculate the whole-body-averaged SAR at frequencies from 10 MHz to 300 MHz at a resolution of 4 mm. Raising an arm above the head increased the SAR value at resonance by up to 35% compared with the standard, arms-by-the-side position.
Wang *et al.* (2006)	Whole-body averaged SAR in adult and child models	Due to the difficulty of measuring SAR in an actual human body exposed to RF-EMF, the incident electric field or power density is often used as a reference. In verifying the validity of the reference level, it is essential to have accurate modelling for humans. A detailed error analysis in the whole-body-averaged SAR calculation was done with the FDTD method in conjunction with the perfectly matched layer (PML) absorbing boundaries. To clarify whole-body-averaged SAR values, a Japanese adult model and a scaled child model were used. The whole-body-averaged SAR under the reference level exceeded the basic safety limit by nearly 30% for the child model, both in the resonance frequency and in the band 2 GHz.
Dimbylow (2007a)	SAR values in voxel models of mother and fetus	An FDTD calculation was conducted of SAR values (20 MHz to 3 GHz) in hybrid voxel-mathematical models of the pregnant female. Models of the developing fetus at 8, 13, 26 and 38 wk of gestation were converted into voxels and combined with the adult female model, at a resolution of 2 mm. Whole-body-averaged SAR in the mother, the average SAR over the fetus, over the fetal brain, and in 10 g of the fetus were calculated.

Table 1.11 (continued)

Reference	Description of the model	Main results and comments
Dimbylow & Bolch (2007b)	Whole-body-averaged SAR in voxel phantoms for a child	Five paediatric phantoms (representing boys aged 9 months, 11 yr and 14 yr, and girls aged 4 and 8 yr) were adapted to calculate the whole-body-averaged SARs in children for plane-wave exposure from 50 MHz to 4 GHz. A comparison was made with previous linearly scaled versions, at a resolution of 2 mm. Further FDTD calculations were performed at resolutions of 1 and 0.7 mm above 900 MHz, to elucidate the effects of variation in grid resolution.
Hirata *et al.* (2003)	Temperature increase in head and brain	The temperature increase (ΔT) in a human head exposed to EM waves (900 MHz to 2.45 GHz) from a dipole antenna was investigated. The maximum ΔT in the head and brain was compared with values from the literature of 10 °C and 3.5 °C for microwave-induced physiological damage. The SAR in the head model was initially calculated by the FDTD method. The ΔT distribution in the head is largely dependent on the frequency of the EM waves, and the maximum ΔT values in the head and brain are significantly affected by the frequency and polarization of the waves. The maximum ΔT in the head (excluding auricles) and brain are determined through linear extrapolation of the peak average SAR in these regions. The peak SAR-1 g should be approximately 65 W/kg to achieve a maximum ΔT of 10 °C in the head, excluding auricles.
Vermeeren *et al.* (2008)	Statistical method to calculate absorption of RF energy	Quantifying the absorption of EM radiation in a human body in a realistic, multipath exposure environment requires a statistical approach, because it needs to be determined for several thousands of possible exposures. To avoid having to make this large number of time-consuming calculations with the FDTD method, a fast numerical method was developed to determine the whole-body absorption in a spheroid human-body model in a realistic exposure environment. This method uses field distributions of a limited set of incident plane waves to rapidly calculate whole-body absorption for any single or multiple plane-wave exposure. This fast method has now been extended to realistic heterogeneous human-body models.
Nagaoka *et al.* (2007)	SAR of a whole-body phantom for pregnant women	A new model for the fetus, including inherent tissues of pregnant women, was constructed on the basis of abdominal MRI data for a woman at week 26 of pregnancy. A whole-body pregnant-woman model was developed by combining the fetus model with a nonpregnant-woman model, developed previously. The model consists of about 7 million cubical voxels (size, 2 mm) and is segmented into 56 tissues and organs. The basic SAR characteristics are presented of the pregnant-woman model exposed to vertically and horizontally polarized EM waves from 10 MHz to 2 GHz.
Nagaoka *et al.* (2008)	SAR for a phantom model of Japanese children	An existing voxel model of a Japanese adult in combination with 3D deformation was used to develop three voxel models that match the average body proportions of Japanese children at age 3, 5 and 7 yr. The models consist of cubic voxels (size, 2 mm) and are segmented into 51 tissues and organs. Whole-body-averaged SARs and tissue-averaged SARs were calculated for the child models, for exposures to plane waves from 30 MHz to 3 GHz.
Togashi *et al.* (2008)	SAR for the fetus in a pregnant-woman model	Dosimetry of EM radiation is described in a pregnant woman in the proximity of a mobile-phone terminal by use of the numerical model of a woman in the seventh month of pregnancy. The model is based on the high-resolution whole-body voxel model of a Japanese adult woman. It is composed of 56 organs, which include the intrinsic organs of a pregnant woman.

Table 1.11 (continued)

Reference	Description of the model	Main results and comments
Conil *et al.* (2008)	SAR for different adult and child models using the FDTD method	Six adult anthropomorphic voxel models were collected and used to build models for children aged 5, 8 and 12 yr, with a morphing method that respects anatomical parameters. FDTD calculations of SARs were performed for frequencies from 20 MHz to 2.4 GHz for isolated models exposed to plane waves. A whole-body-averaged SAR, average SARs on specific tissues such as skin, muscles, fat or bones, and the average SAR on specific parts of the body such as head, legs, arms or torso, were calculated. The SD of the whole-body-averaged SAR of adult models can reach 40%. For adults, compliance with reference levels ensures compliance with basic restrictions. For children, the whole-body-averaged SAR exceeds the fundamental safety limits by up to 40%.
Kühn *et al.* (2009b)	Assessment of induced EMFs in various human models	The absorption characteristics are given for various anatomies ranging from a child aged 6 yr to a large adult male, by numerical modelling, with exposure to plane waves incident from all six major sides of the humans with two orthogonal polarizations each. Worst-case scattered-field exposure scenarios were constructed to test the implemented procedures of current in situ compliance measurement standards. The results suggest that the reference levels of current EM safety guidelines for demonstrating compliance, as well as some of the current measurement standards, are not consistent with the basic restrictions and need to be revised.
Neubauer *et al.* (2009)	SAR and EMF intensity for heterogeneous exposure	The relation between the incident EMF strength, the wbSAR, and the local SAR, was investigated for heterogeneous exposure scenarios at mobile communication frequencies. For whole-body exposure at 946 MHz, 12% of all heterogeneous cases examined represent worse exposure conditions than plane-wave exposure. This percentage increases to 15% at 1840 MHz, and to 22% at 2140 MHz. The results indicate the need to extend investigations to numerical simulations with additional human phantoms representing parts of the human population having different anatomy and morphology compared with the phantom used here. This also applies to phantoms of children.
Hirata *et al.* (2009)	Whole-body-averaged SAR in children	The whole-body-averaged SAR was calculated in an infant model with the FDTD method, and the effect of polarization of incident EM waves on this SAR was investigated. The whole-body-averaged SAR for plane-wave exposure with a vertically aligned electric field is smaller than that with a horizontally aligned electric field for frequencies above 2 GHz. The main reason for this difference is probably the component of the surface area perpendicular to the electric field of the incident wave.
Nagaoka & Watanabe (2009)	Estimation of SAR in different models for children	To estimate individual variability in SAR for children of different age and with different physical features, a large set of 3D body-shape data from actual children aged 3 yr was used to develop several homogeneous models of these children. The variability in SAR of these models of whole-body exposure to RF-EMF in the VHF band was calculated by the FDTD method.
Findlay *et al.* (2009)	SAR for voxel models for children in different postures	SAR calculations were performed on two voxel models (NORMAN, ETRI) for a child aged 7 yr in different postures (standing with arms down, standing with arms up, sitting) for plane-wave exposure under isolated and grounded conditions between 10 MHz and 3 GHz. There was little difference at each resonant frequency between the whole-body-averaged SARs calculated for the two models for each of the postures studied. However, compared with the arms-down posture, raising the arms increased the SAR by up to 25%.

Table 1.11 (continued)

Reference	Description of the model	Main results and comments
Kühn *et al.* (2009b)	SAR induced in the human head from mobile phones used with hands-free kits	To determine the extent to which the use of wired and wireless hands-free kits can reduce human exposure, the SARs from these kits were determined experimentally while connected to mobile phones (GSM900/1800, UMTS1950) under maximized current coupling onto the cable and various wire-routing configurations. The maximum psSAR in the head when using wired hands-free kits was more than five times lower than current recommended limits. The SAR in the head depends on the output power of the mobile phone, the coupling between the antenna and cable, external attenuation and potential cable-specific attenuation. In general, a wired hands-free kit considerably reduces the exposure of the entire head region compared with mobile phones operated at the head.
Gosselin *et al.* (2009)	Human exposure in the close vicinity of mobile-phone base-station antennae	Human exposure in close vicinity of mobile-phone base-station antennae was assessed by means of FDTD simulations. The peak spatial average SAR and the whole-body-averaged SAR were calculated for three different anatomical models (55–101 kg) at distances between 0.5 and 4 m from various antenna types, at frequencies of 450–2140 MHz. The whole-body absorption generally determines the maximum permissible output power for collinear array antennae. In particular for short antennae, the peak spatial average SAR can be more restrictive than the whole-body absorption because they may only expose a fraction of the body.
Vermeeren *et al.* (2010)	SARs in a phantom for a human male exposed to representative base-station antennae	The variation in whole-body and peak spatially averaged SARs was determined for the heterogeneous "virtual family" male model placed at 30 cm, 1 m, 3 m and 10 m in front of different base-station antennae in a reflective environment. SAR values were also compared with those in the free-space situation. The six base-station antennae operated at 300 MHz, 450 MHz, 900 MHz, 2.1 GHz, 3.5 GHz and 5.0 GHz, respectively. The ratio of the SAR in a reflective environment and the SAR in the free-space environment ranged from −8.7 dB up to 8.0 dB.
Uusitupa *et al.* (2010)	SAR variation for 15 voxel models including different postures	A study on SARs covering 720 simulations and 15 voxel models (body weight range, 18–105 kg) was performed by applying the parallel FDTD method. The models were irradiated with plane waves (300 MHz to5 GHz) with various incoming directions and polarizations. For an adult, the effect of incoming direction on wbSAR is larger in the GHz range than at around 300–450 MHz, and the effect is stronger with vertical polarization. For a child (height, ~1.2 m), the effect of incoming direction is similar as for an adult, except at 300 MHz for horizontal polarization. Body posture has little effect on wbSAR in the GHz range, but at around 300–450 MHz, a rise of 2 dB in wbSAR may occur when posture is changed from the standing position. Between 2 and 5 GHz for adults, wbSAR is higher for horizontal than for vertical polarization. In the GHz range, horizontal polarization gives higher wbSAR, especially for irradiation from the lateral direction. A homogenized model underestimates wbSAR, especially at approximately 2 GHz.
Kawai *et al.* (2010)	Computational dosimetry of SAR in models of embryos of different age	SAR dosimetry is presented in models of pregnant (4 and 8 wk) Japanese women, with a cubic (4 wk) or spheroidal (8 wk) embryo, exposed to plane waves at frequencies of 10 MHz to 1.5 GHz. The averaged SARs were calculated in the embryos exposed to vertically and horizontally polarized plane waves. The maximum average SAR in the exposed embryos is < 0.08 W/kg when the incident power density is at the recommended environmental level for the general public.

3D, three-dimensional; ANSI, American National Standards Institute; EMF, electromagnetic field; EU, European Union; FDTD, finite-difference time-domain; IEEE, Institute of Electrical and Electronic Engineers; mo, month or months; MRI, magnetic resonance imaging; psSAR, peak spatial SAR; PML, perfectly matched layer; RF, radiofrequency; SAM, specific anthropomorphic mannequin; SAR, specific absorption rate; sSAR, spatially averaged SAR; SD, standard deviation; VHF, very high frequency; wbSAR, whole-body SAR; wk, week or weeks; yr, year or years

For a summary of studies with models for partial- or whole-body exposure, see Tables 1.10 and 1.11.

1.4 Measurement techniques

1.4.1 Introduction

Assessment of the incident exposure is simple for plane-wave or far-field conditions. Unfortunately, when high exposures are involved, far-field conditions rarely occur, due to the proximity of the source. In addition, the reflecting environments result in fading, producing fields that are highly variable spatially and temporally.

In general, far-field conditions are approximately met locally by changing the amplitude in space at distances larger than the extension of the reactive near-field zone (CENELEC, 2008):

Thus, for distances meeting the requirements of the equation, only the maximum of the field components must be determined to demonstrate compliance. For any distance smaller than the requirements of the equation, the maximum of both components must be spatially scanned to reliably predict that the maximal induced fields are below a certain limit. Fine volume scanning of transmitting antennae in the very near field yields greater uncertainty, neglects reflection back to the source antenna due to the presence of a lossy body, and is more time-consuming than dosimetric measurements in homogeneous phantoms. Since such near-field assessments are more conservative, they are rarely conducted in the context of exposure assessments.

In summary, reference levels are easy to assess if the plane-wave or far-field conditions are approximately met (see Section 1.3.2) and the resulting SAR and induced current densities are below the corresponding basic restrictions under all circumstances. The reference limits for occupational/controlled and for the general public/uncontrolled exposure are given in NCRP (1986), ANSI/IEEE (1991, 2002b) and ICNIRP (1998). However, sometimes only the incident electric field (E-field) or the E-field-based equivalent power density is also reported for cases in which the above equation is not satisfied and therefore may not well represent true exposure. It should also be noted that the maximum value that is often reported is suitable for reporting compliance with guidelines, but may greatly overestimate typical exposures at that location.

1.4.2 Near-field and dosimetric probes

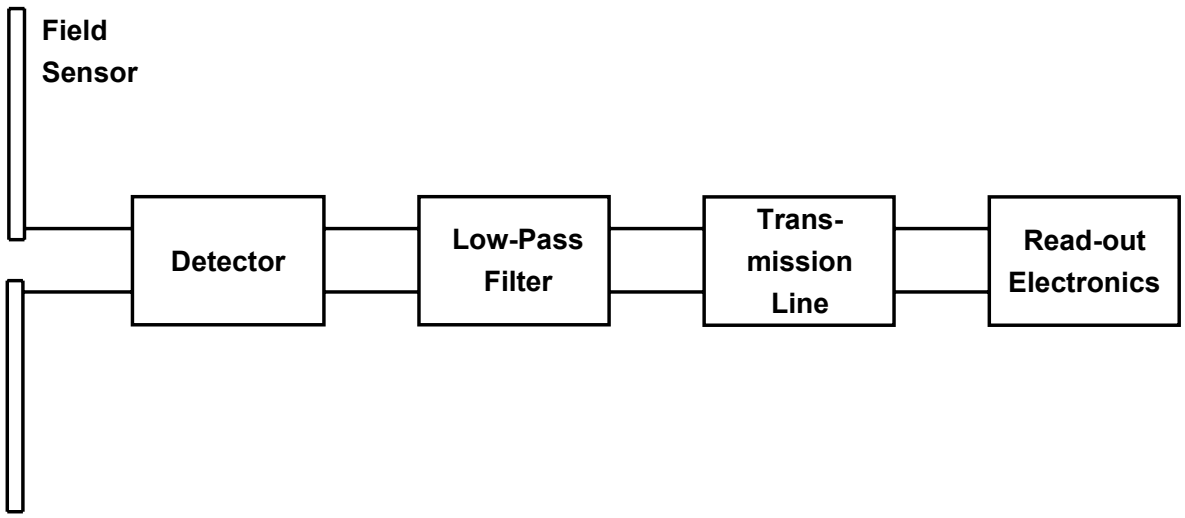
The first instruments were developed in the early 1970s and they covered the 10 MHz to 10 GHz region of the spectrum. One involved the use of two pairs of thin-film thermo-coupling vacuum-evaporated electrothermic elements that functioned as both antenna and detector (Aslan, 1970). In another instance, two small diode-loaded dipoles were employed as sensor elements (Rudge, 1970). In 1975, the first prototype of an isotropic, miniature field probe was introduced (Bassen *et al.*, 1975). Fibre-optic field probes were proposed as early as the 1970s (Bassen *et al.*, 1977). Comprehensive overviews of field probes have been published (Bassen & Smith, 1983; Poković, 1999).

(a) Broadband E-field probes

Diode-based field probes are most commonly used for dosimetric assessments. These instruments consist of field sensors, a detector, transmission lines and readout electronics (Fig. 1.14). The probe is constituted of three mutually orthogonal diode-loaded dipoles with an isotropic receiving pattern. Different orthogonal sensor configurations are available.

An RF detector Schottky-type diode is placed at the centre of the dipole sensor. If the detector diode operates in the square-root law region, the detected voltage is proportional to the RF power. The data-acquisition electronics are connected to the detector diodes by high-resistance transmission lines to minimize incident-field perturbation

Fig. 1.14 Simplified schematic of a broadband-field probe



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and spurious pick-up effects. A detailed investigation of transmissionline design can be found in Smith (1981).

Magnetic-field (H-field) probes are also available; the basic theory on which such probes are designed can be found in Whiteside & King (1964). H-field probes and E-field probes have similar features except that H-field probes employ a small loop element instead of a dipole sensor. Loop-based sensors present the disadvantage of a strong frequency dependence and induction of currents by both H- and E-fields. Different methods for flattening the frequency response of loop probes have been suggested (Kanda, 1993; Poković, 1999). Lossy covers have been proposed to further suppress the E-field sensitivity of the loop (Poković, 1999).

A general problem of diode-based probes is their inherent nonlinearity over their dynamic range. Methods to overcome these limitations are presented in Kühn *et al.* (2007b).

Unlike diode-based sensors, thermocouple probes are true square-law detectors. Such sensors are particularly useful in free-space field surveys (Narda STS, 2005). These sensors are, however, impractical for dosimetric and near-field measurements because of their size, generally lower sensitivity and dynamic range.

Thermistors are also small true square-law detectors. They can have a higher resolution than thermocouples, but need more frequent calibration.

The performance of these probes depends strongly on the following parameters:

- Frequency, modulation, and field strength;
- Polarization, direction of propagation, and field gradients;
- Material boundaries near the probe sensors;
- Sources of interference (noise, static and low-frequency fields, vibration, temperature, etc.).

The influence of these parameters must be characterized by individual calibration under well-defined conditions for each probe. A detailed summary of different calibration methods for field probes and a characterization of the most crucial parameters contributing to the measurement of uncertainty are given in Poković (1999). The influence of these parameters must

be included in the resulting uncertainty assessment, since the conditions of actual use of the probes may differ considerably from the conditions under which they are calibrated.

Modern free-space and dosimetric field probes operate in the frequency band from 10 MHz up to 6 GHz. They have an isotropy error smaller than ± 0.5 dB and sensitivities in the range 5–10 μW/g. These probes have very small sensor tips (2.5 mm) to allow high spatial resolution and measurements very close to material boundaries. A probe with reduced size (tip diameter, 1.0 mm) has been described for accurate dosimetric measurements at frequencies exceeding 10 GHz (Poković *et al.*, 2000a). Probes for determining both the electrical- and magnetic-field pseudo-vector information are presented in Poković *et al.* (2000b).

(b) Electro-optical sensors

Modern, electro-optical sensors allow the measurement of the full RF-frequency domain and phase as well as intermediate-frequency time-domain signal information while maintaining a superior electrical isolation through the use of optical fibres for signal transmission.

In general, two sensor concepts are used today: (1) passive optical sensors (Togo *et al.*, 2007); and (2) active optical sensors Kramer *et al.* (2006). Modern passive electro-optical sensors typically modulate the information on laser light passing through electro-optically active crystals embedded in a fibre-optic system. Common crystal materials include cadmium telluride (CdTe) and lithium niobate ($LiNbO_3$), which change their refractive indices depending on the E-field applied across the crystal, or cadmium manganese telluride (CdMnTe), which is sensitive to the magnetic fields applied across the crystal (Poković, 1999). The sensitivities of modern active optical sensors can be as low as 100 μV/m per Hz^2, or greater than 0.3 V/m when measuring a signal of width of 5 MHz (Kramer *et al.*, 2006).

1.4.3 Measurement antennae

Different types of broadband-matched antennae are usually applied for the frequency-selective exposure assessment of incident fields. These broadband antennae are matched to 50 ohm to be compatible with standard RF receivers. They have applications in far-field measurement of radiation, e.g. from cellular base stations and broadcast services.

Common broadband RF-measurement antennae such as horn or log-periodic antennae have a certain directivity. This reduces the applicability of these antennae for complex propagation scenarios, particularly at locations where the incident field is not dominated by a direct line-of-sight propagation path, but by multipath propagation (Kühn, 2009).

Tuned dipole antennae have an isotropic pattern (no directivity) in azimuth, but lack broadband characteristics.

Conical dipole antennae have an isotropic pattern in azimuth and generally good broadband characteristics (Seibersdorf Research, 2011), which substantially reduces the number of measurements needed.

1.4.4 Temperature instrumentation

(a) Temperature probes

Local SAR values can also be assessed by temperature measurements (see Section 1.3); however, thermal-diffusion effects must be practically absent. This is only possible if the system is in thermal equilibrium at the beginning of the exposure, or if heat-diffusion processes are known for the assessment period. Heat losses due to radiation and convection during the measurement interval must be negligible, or known and corrected for. If these heat-diffusion processes are unknown, the response time of the thermal measurement equipment must be sufficiently short to avoid underestimation of the exposure (Schuderer *et al.*, 2004a).

Two types of temperature probes exist: thermistor-based and those based on optical effects. The requirements for temperature probes for SAR assessments are:

- Small size: the probe must be small to resolve high temperature gradients, without disturbing the temperature distribution or the RF field;
- Non-conductive materials: only electrically non-conductive materials prevent heating of the probe by induced currents because they are transparent to EMFs;
- Low noise level: small differences in temperature must be detected accurately, especially for dynamic temperature measurements, e.g. of SAR, and thus the noise level should be much less than 10 mK;
- Short response time: this is essential for SAR measurements as the temperature rise (dT/dt) is proportional to the SAR only in the absence of heat diffusion. A probe suitable for SAR measurements must have reaction times much faster than 100 ms (Schuderer *et al.*, 2004a).

A novel design for temperature probes for dosimetric assessments, introduced by Schuderer *et al.* (2004a), provides a spatial resolution of 0.02 mm^2, a noise level of the temperature of 4 mK, and a sensitivity of 0.5 mK/s with a response time of < 14 ms.

Temperature probes based on thermo-optical effects are applied in high-voltage transformers, industrial microwave ovens and in treatment for hyperthermia. One exploited effect is the decay rate of a phosphorescent layer at the tip of a fibre-optic cable (Wickersheim & Sun, 1987). These commercially available probes have a noise level of 0.1 K, with reaction times of 250 ms. Another optical effect is the interferometric property of a cavity filled with materials that have highly temperature-dependent refractive indices. These probes reach sensitivities of 2–3 mK/s (Burkhardt *et al.*, 1996).

(b) Infrared photography

The measurement of temperature by black-body-equivalent radiation (infrared photography) is an alternative to invasive measurements using temperature probes. The resolution of infrared thermographs can be very high and the sensitivity of affordable infrared detection systems has improved substantially over the past 30 years. This was also one of the first methods used to measure SAR (Guy, 1971), as the surface radiation can be recorded quickly with infrared cameras without perturbing the incident field. Infrared cameras were used to measure the temperature increase on a human head exposed to GSM mobile phones (Taurisano & Vander Vorst, 2000). The technique has several disadvantages:

- Limited sensitivity compared with temperature or dosimetric probes;
- Can be used only for measurements of surface temperature;
- The thermal radiation characteristics of the materials must be determined accurately;
- The background radiation must be homogeneous;
- Evaporation and convection can cause substantial errors and must be controlled;
- Different viewing angles of the camera can yield different results, since surfaces are not isotropic infrared radiators.

(c) Microcapsulated thermo-chromic liquid crystals

A novel idea to assess three-dimensional temperature distributions optically and in quasi real-time was proposed by Baba *et al.* (2005). Microcapsulated thermochromic liquid crystals (MTLC) were suspended uniformly in a gel with the dielectric properties of human muscle tissue. The temperature of the gel is determined by measuring the light scattered from a laser beam

that scans through the liquid. The technique has limited dynamic range and sensitivity.

(d) Calorimeters

Calorimetry encompasses methods for measuring heat produced by biological, chemical or physical endothermic or exothermic processes. Calorimetric methods are suitable for determining average wbSAR, but they cannot provide information about SAR distribution.

Calorimetry can be subdivided into two types:

- Direct calorimetry: the heat is measured directly by use of calorimeters;
- Indirect calorimetry: the quantity of heat is determined by measuring the amount of oxygen consumption and relating it to the oxicaloric equivalent of the reaction.

Basically, calorimetric dosimetry analyses the heating and cooling processes of a sample exposed to RF radiation. Typical direct calorimeters used in microwave dosimetry are the Dewar flask and the twin-well calorimeter (Gajsek *et al.*, 2003).

1.4.5 Measuring SAR and the near field

Dosimetric evaluation inside test phantoms such as SAM requires the measurement of SAR at several hundreds of points distributed over a complex three-dimensional phantom. The process is divided into: (1) searching for the location of the maximum absorption on a two-dimensional grid; and (2) determining the psSAR value on a fine three-dimensional grid. These points must be determined with high accuracy, especially at high frequencies, to achieve low measurement uncertainty despite high attenuation and large variations in spatial-field intensity. Automated systems for dosimetric assessment have been developed to perform these compliance tests. A typical system for dosimetric assessment is a computer-controlled six-axis robotic positioner. It is used to move the dosimetric E-field probe within a scanning grid, which can be adaptive, e.g. it follows the surface that is being detected during the scanning job and positions the probe axis orthogonal to that surface. The measurement results, i.e. field and SAR distributions, as well as 1 g and 10 g spatial average peak SAR, are automatically evaluated and visualized. The expanded standard uncertainty (k = 2) is less than 20%. It should be noted that this approach provides reliable conservative estimates of the maximum peak spatial SAR that might occur in the user population, but offers little information about the exposure of specific tissues or individual exposure (Kühn, 2009).

In summary, compliance evaluation of body-mounted transcievers provides reliable conservative estimates of maximum psSAR-1 g and psSAR-10 g anywhere in the body, but these estimates are generally poorly correlated with the maximum exposure of specific tissues (e.g. brain tissue) or typical exposure levels during daily usage of the device (system- and network-dependent). In other words, the information has only limited value for epidemiological studies.

1.4.6 Incident-field measurements in the far field

Evaluation of the exposure in the far field of a transmitter is usually conducted for fixed installations such as radio and television broadcast antennae, radar sites, or cellular base stations. Exposure assessments are carried out in areas that are generally accessible or for which access is restricted to qualified working personnel only. Compliance is tested with respect to the reference levels by assuming free-space field impedance for the RF energy, i.e. by E-field evaluation. Only one measurement point is required under real far-field conditions. However, actual environments usually involve nearby reflectors and scatterers, i.e. a scanning procedure is required to find the maximum incident fields (Kühn, 2009).

Since the transmitters under evaluation do not always operate at maximum power – the transmitted power of base stations being dependent on traffic intensity – broadband instantaneous measurements are often insufficient to determine the highest level of exposure. In such cases, information on the maximum exposure with respect to the measured values must be available and soundly applied to establish exposure in the worst-case scenario. Table 1.12 lists the parameters necessary for extrapolation of exposure in the worst case and to reduce the uncertainty of the actual measurement campaign. It is easier to determine the measurement methods when additional parameters are known. General sources of error are:

- Field perturbation by measurement personnel, e.g. scattering and absorption of EMFs due to the body of the measurement engineer;
- Application of an inappropriate measurement antenna, e.g. disregard for antenna directivity and polarization;
- Application of ineffectively decoupled cables, acting as secondary antennae;
- Application of incorrect measurement settings of the RF receiver for the type of signal to be measured;
- Incorrect selection of the measurement location, e.g. measurement points that are not appropriate for yielding the maximum EMF exposure or measurement points close to bodies that influence the calibration of the measurement antennae (Kühn, 2009).

Different methods for assessing EMF exposure in the far field have been proposed. One approach is the antenna-sweeping method. This method requires the engineer to slowly move the measurement antenna with varying polarizations and directions through the volume of interest (Sektion NIS, 2002). Another method is based on the examination of several well defined points in the area of interest. In this case, the antenna is mounted on a tripod and the different directions and polarizations are examined at the considered points (ANFR, 2004). The first method is conservative, but sensitive to the position of the operator with respect to the antenna. With the second method, measurements can be performed with the engineer located further away, but the number of measurements in the volume is small. A combination of both methods is presented by Coray *et al.* (2002), who suggest that the region is first scanned for the field maximum in the area of interest and that an isotropic and frequency-selective measurement is then performed at the location of the maximum.

Often, far-field techniques are employed in the near field of transmitters, e.g. on transmitter towers. Some standards allow a spatial averaging of E-field evaluations (ANSI/IEEE, 1991), the rationale of which is based on the wbSAR limit. However, this constitutes a relaxation of the safety criteria as it does not consider H-field coupling as the dominant mechanism in the near field nor the limits of psSAR. On the basis of current knowledge, such relaxations do not exclude the possibility of exceeding the basic restrictions or underestimating the local exposure (Kühn, 2009).

The advantages and limitations of different measurement equipment for assessing the exposure of unknown transmitters are discussed below.

1.4.7 Broadband measurements

Broadband-measurement probes are single-axis or three-axis sensors (dipole or loop) constructed in a similar way to the near-field sensors. No information on the spectral characteristics of the field is provided by these probes. Therefore, if a broadband meter is used for compliance testing, the measured field value must be no higher than the lowest permissible limit defined for the frequency range of the meter. Broadband survey meters are also

Table 1.12 Important parameters of radiofrequency transmitter sites assessed in the far field

Site parameter	Explanation
Location	The location of the transmitter with respect to the measurement point
Line of sight/nonline of sight	Determines if a prevalent propagation path may be expected
Type of site	Single or multiple antenna site
Antenna directivity	Antenna beam characteristics
Antenna radiation direction	The direction of maximum radiation
Antenna power at measurement	The antenna input power at the time the measurement takes place
Maximum antenna input power	Maximum permissible antenna input power
Frequency	Frequencies at which the site transmits
Communication system	Communication system that is used, i.e. which signal modulation characteristics are to be expected
Other sources of radiation	The field at the measurement points when the assessed transmitter is switched off

Adapted from Kühn (2009)

relatively inexpensive and easy to use, and are thus often used for field-survey measurements (Kühn, 2009).

Fig. 1.15 displays the components of typical broadband field-survey meters. Fig 1.16 shows the frequency response of two broadband probes.

Some broadband probes are designed to match the frequency dependence of the human exposure limits. In all cases, it is advised that the out-of-band response of these instruments is carefully characterized to avoid spurious readings. If a specific transmitter is the dominant source, compliance testing is substantially simplified (CENELEC, 2005).

The main sources of uncertainty regarding broadband survey meters are: calibration, linearity, frequency response, isotropy, time-domain response, and temperature response; so the accuracy of broadband evaluations is significantly limited, but generally conservative (Kühn, 2009).

(a) Frequency-selective measurements

Frequency-selective measurement techniques can overcome the difficulties of the unknown spectrum of the field. However, the execution of the measurement is more complicated and requires specialized engineers.

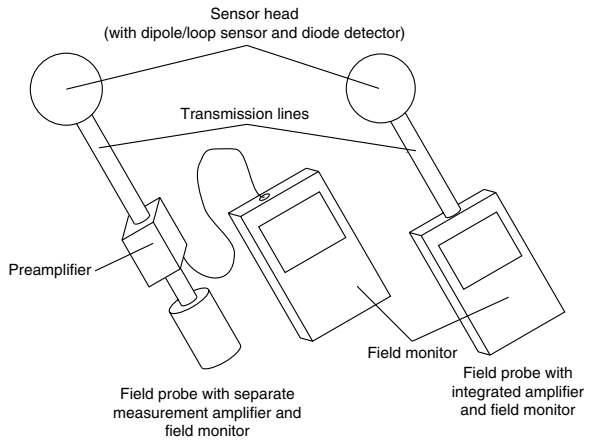
Measurements in the frequency domain are performed with an antenna connected to a spectrum analyser.

Most spectrum analysers provide video filters for additional smoothing of the spectral signal. Optimal parameter settings for the analyser for GSM and UMTS based on a simulation approach have been presented (Olivier & Martens, 2005, 2006). The application of spectrum analysers is a complex topic. Procedures dealing with frequency-selective measurements should always describe the parameter settings of the spectrum analyser to produce correct, reproducible and comparable results. Nevertheless, the engineer should test the actual applicability of these settings for the particular measurement equipment (Kühn, 2009).

The main sources of uncertainty regarding frequency-selective measurements are:

- Calibration of the spectrum analyser, cable, and measurement antenna;
- Linearity of the spectrum analyser, cable, and measurement antenna;
- Frequency response of the spectrum analyser, cable, and measurement antenna;
- Demodulation method of the spectrum analyser (detector type);

Fig. 1.15 Schematic of the most common broadband radiofrequency field-survey meters



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- Temperature response of the spectrum analyser, cable, and measurement antenna; and
- Mismatch between measurement equipment.

Although frequency-selective measurement methods overcome most of the problems affecting use of broadband-survey meters, they are not always sufficient to correctly evaluate exposure from different transmitters operating at the same frequency. In this case, measurement receivers should be applied (Kühn, 2009), as presented below.

(b) Code-selective measurements

Code-selective measurements are specifically necessary when the exposure from a transmitter involves code-division multiple access (CDMA), e.g. when a Universal Mobile Telecommunications System (UMTS) is to be assessed. All UMTS base stations usually transmit in the same frequency band. With a frequency-selective receiver, it is not possible to discriminate between exposures from different base stations, because a single frequency band is used and the channels are multiplexed in the code domain. Code-selective receivers decode the signal received from a base station, i.e. the receiver is able to discriminate between the received field strength from its base station and other noise-like sources. The receiver measures only the field received from its transmitting base station if the particular descrambling code is used for decoding. Basically, the same sources of uncertainty must be considered for code- and frequency-selective measurements. In general, if measurement receivers are applied, the overestimation of the measured field values is expected to be smaller than for frequency-selective and broadband measurements (Kühn, 2009).

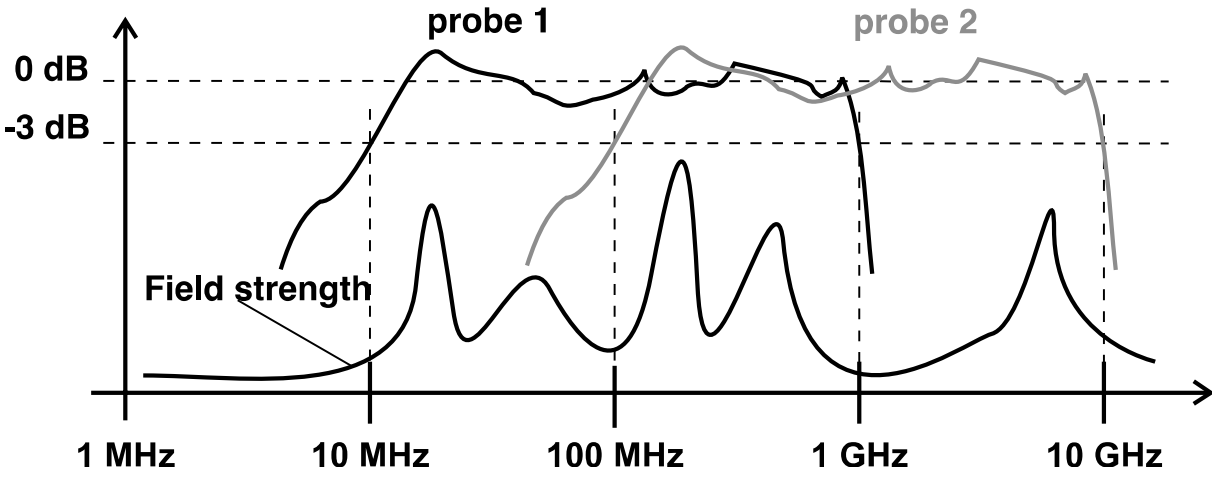
1.4.8 Calibration

Measurement with known uncertainty can only be performed if the measurement equipment is appropriately calibrated. In general, calibration of the measurement equipment is demanding (sensitivity as a function of frequency and modulation, linearity for different modulations, deviation from isotropy, etc.). High-quality calibration documentation is essential to determine the accuracy of the measurements or their uncertainty, respectively.

1.4.9 Uncertainty assessment

Exposure assessments are prone to many uncertainties that must be carefully determined. This is the most difficult aspect of any measurement protocol, because it usually covers many more parameters than only the uncertainties associated with the measurement equipment. For example, in the case of demonstration of compliance with respect to basic restrictions, it includes estimation of the coverage factor for the exposed populations. In the case of uniform incident field, it is necessary to determine the uncertainty of the field measured during the period of measurement with respect to the maximum exposure at this site. In case of non-uniform fields, it needs to

Fig. 1.16 Frequency response of two broadband radiofrequency field-survey meters



The fields in the frequency ranges are summed. If the outputs from probes 1 and 2 are added, then the fields in the overlapping frequency range are counted twice. The field values measured with probe 1 must comply with the lowest limit in the frequency band 10 MHz to 1 GHz, while the readout of probe 2 must comply with the lowest limit between 100 MHz and 10 GHz. The overlapping frequency range is surveyed twice if the exposure values are superimposed to cover the entire frequency range.
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be demonstrated that the ratio of measured fields to reference levels is conservative with respect to the induced fields.

[The Working Group noted that it should be good measurement practice for the results of any measurement campaign to be presented only when accompanied by an extensive uncertainty assessment.]

1.4.10 Specific measurement problems

(a) Demonstration of compliance with dosimetric safety limits

The objective of compliance demonstration is to determine the exposure conservatively for the range of intended usage of the device or equipment with respect to the entire user group. In general, there is a strong dependence on position, distance, anatomy and posture. This dependence can only be determined by numerical simulations. Given an acceptable uncertainty, several hundred permutations of the most important parameters must be performed. In other words, the parameter space is large and the assessment must be done with sufficient care and followed by an extensive discussion on the parameters investigated and the resulting uncertainties.

(b) Assessing personal exposure

In its most recent update of *Research Agenda for Radiofrequency Fields*, the World Health Organization (WHO) has recommended improvement of exposure assessment in epidemiological studies as a high-priority research need: "Quantify personal exposures from a range of radiofrequency sources and identify the determinants of exposure in the general population" (WHO, 2010a).

Associated problems with personal exposure assessment are:

- Compliance tests versus real-life exposure;
- Assessment of incident versus induced fields;
- Appropriate dosimetric quantities;
- Combination of exposure from multiple sources operating at different distances and frequencies;

- Strong temporal, geographical and usage dependence of the exposure, especially in relation to the exposure period relevant to the epidemological data;
- Technology dependence of exposure and rapid technological changes; and
- Selection and, even more importantly, exclusion of potential exposure proxies.

As mentioned before, the worst-case levels of exposure determined during compliance testing of, e.g. mobile phones or base stations are in many cases not representative of actual real-life and everyday exposure. The protocols for compliance testing are generally optimized to provide a conservative estimate of maximum exposure. However, exposure assessment in epidemiological research aims at categorizing actual personal exposure. Results from compliance testing can, however, be useful to validate propagation models (Bürgi *et al.*, 2008), or to compare potential proxies that can be independently assessed, such as those based on mobile-phone design (Kühn, 2009).

Assessment and dosimetry of EMF exposure in epidemiological and human studies have been and often still are performed in terms of quantities that are only representative for demonstration of compliance with safety guidelines, e.g. incident-field quantification, or induced wbSAR and psSAR. The dosimetric meaning of the aforementioned quantities is questionable for current studies, which all aim at detecting potential effects for exposures well below established safety levels. In addition, the end-points investigated are typically effects on specific tissues, organs or functional regions of the brain and the quantification of the classical dose evaluations often does not allow a clear distinction between body regions or an accumulation of the dose from various sources. Quantification of exposure in terms of incident fields is especially problematic, since incident fields are often not directly related to induced fields. A common mistake is to combine exposure in terms of incident fields at different frequencies by applying the root-sum-square (see Glossary) over the individual frequency contributions. Currently, novel dosimetric models are being developed to relate incident to induced EMF (Djafarzadeh *et al.*, 2009) or to relate SAR-compliance test data measured in homogeneous media to SAR in specific anatomical regions of the human brain (Gosselin *et al.*, 2011). By expressing exposure directly in terms of induced EMF or SAR in specific regions, the combination of multiple sources also becomes straightforward. Also, it allows a direct assessment of different source contributions according to geographical location or usage.

Variations due to geographical location in the far-field of transmitters should only be addressed with validated propagation models (e.g. Andersen *et al.*, 2007; Frei *et al.*, 2009a), and not with, e.g. simplistic distance metrics. For near-field exposure, e.g. from mobile phones, the orientation of the source with respect to the body is relatively well defined; however, due to the output power control of modern mobile devices, there can be large variation in exposure depending on geographical location (more than twofold) and, even more importantly, the communication system (a factor of 100 or more). The assessment of these variations is typically addressed in terms of measurements in situ (Wiart *et al.*, 2000; Kühn, 2009; Kelsh *et al.*, 2010).

(c) Measurement of the very close near field below 10 MHz

The assessment of human exposure at frequencies between 30 MHz and 6 GHz is well established. International standards and national guidelines provide detailed assessment methods that are well specified with relatively low uncertainty. The measurement of incident fields at frequencies below 10 MHz is also well established. However, there is comparatively little research on the measurement of induced fields at frequencies below 10 MHz. The problems

associated with induced-field measurement at frequencies below 10 MHz include:

- Strong spatial non-uniformity of the fields, requiring high resolution of measurements;
- Strong temporal variation in the fields, especially from signals with transients, requiring equipment to have a large operating bandwidth;
- Field values measured very close to the source greatly overestimate the induced values, i.e. compliance often needs to be demonstrated by assessment of the induced fields;
- High variation in the permittivity and conductivity of tissues, making human modelling (e.g. development of phantoms) difficult;
- Practical limitations in the use of time-domain numerical electromagnetic solvers at low frequencies, resulting in slow convergence; and
- Limitations in the applicability of certain frequency-domain numerical electromagnetic solvers (e.g. electro-quasistatic solvers) due to assumptions and approximations.

(d) Measurement of signals with complex modulations

Today, most broadband field probes, as well as personal exposure meters, are calibrated with narrow-band (single-frequency) continuous wave signals. However, the measured signals differ greatly from continuous wave signals in terms of variation in time-domain amplitude and signal bandwith. Variation in the time-domain amplitude of modern communication signals (peak-to-average power ratio [PAPR] of up to 14) places great demands on the linearity of the detectors in broadband probes and exposure meters, and in spectrum analysers. These requirements are often not fulfilled for the detectors and filters in traditional field probes and exposure meters, such that these respond differently when comparing continuous wave and waveforms applying modern modulation schemes. For compliance testing, field probes can be calibrated with the actual test signals. For measurements in situ, e.g. with exposure meters, such a calibration is not straightforward since the real-life communication-signal characteristics might not always remain constant during measurement. Care should be taken also when using narrow-band receivers, i.e. spectrum analysers, when measuring complex-modulation waveforms. Also, these receivers require modulation-specific measurement settings, e.g. filter, detector, resolution bandwidth, sweep time etc. to perform field measurements with reasonably small uncertainties (Joseph *et al.*, 2002, 2008; Olivier & Martens, 2005, 2006).

1.5 Interaction of RF-EMF with biological systems

Although numerous experimental studies have been published on the non-thermal biological effects of RF-EMF, multiple computational analyses based on biophysical and thermodynamic considerations have concluded that it is theoretically implausible for physiological effects (except for reactions mediated by free radical pairs) to be induced at exposure intensities that do not cause an increase in tissue temperature (Foster, 2000; Adair, 2002, 2003; Sheppard *et al.*, 2008).

RF electromagnetic radiation is classed as non-ionizing radiation as it comprises photons that do not have sufficient energy to break chemical bonds or ionize biological molecules (Stuchly, 1979). The energy of a photon of an electromagnetic wave is given by $E = hf$, where h is Planck's constant (6.626×10^{-34} J•s or 4.136×10^{-15} eV•s) and f is frequency, thus the energy of a photon in the RF spectrum varies from approximately 4.1×10^{-6} eV (6.6×10^{-25} J) at 1 GHz to 1.2×10^{-3} eV

(2.0×10^{-22} J) at 300 GHz. This is thus far less than the minimum amount of energy needed to ionize organic materials or metals, which is approximately 5–10 eV.

When a biological body (animal or human) or tissue is exposed to an RF-EMF, the RF energy is scattered and attenuated as it penetrates body tissues. Energy absorption is largely a function of the radiation frequency and the composition of the exposed tissue. Because of the high dielectric constant of water, the water content of the tissue determines to a large extent the penetration of a frequency-specified electromagnetic wave. The rate of energy absorbed by or deposited per unit mass per unit time is the specific absorption rate (SAR); this value is proportional to the root-mean-square (rms) of the induced electrical field strength $[E]^2$ and to the electrical conductivity (σ) of the tissue per tissue density (ρ):

$$SAR = [E]^2 \cdot \sigma/\rho$$

The SAR expressed in units of watts per kilogram (or mW/g) can also be estimated from measurements of the rise in temperature caused by RF-energy absorption in tissue:

$$SAR = C_p \cdot \delta T/\delta t$$

where C_p is the specific heat of the tissue or medium, $\delta T/\delta t$ is the initial rise in temperature over time. Values for the dielectric constant and conductivity vary substantially over the RF range (30 MHz to 300 GHz).

To cause a biological response, the EMF must penetrate the exposed biological system and induce internal EMFs. RF-energy absorption depends on incident field parameters (frequency, intensity, polarization), zone of exposure (near field or far field), characteristics of the exposed object (size, geometry, dielectric permittivity and electric conductivity), and absorption or scattering effects of objects near the exposed body (Stuchly, 1979).

Based on the relationship between wavelength (λ) and frequency

$$c = f \cdot \lambda$$

where c is the speed of light (3×10^8 m/s), it is obvious that the wavelength of RF radiation varies substantially between 30 kHz (10 km) and 300 GHz (0.1 cm). At the frequencies used for mobile phones (approximately 1–2 GHz), the corresponding wavelengths are 30 and 15 cm. Considering that near-field exposures occur at distances from a radiating antenna within approximately one wavelength of the radiated EMF and that far-field exposures occur at distances that exceed one wavelength of the radiated EMF, it is clear that reactive near-field and far-field exposures may occur, depending on the frequency of the incident field and the distance of the exposed person from the radiating antenna. Both near-field and far-field exposures can occur with the use of wireless telecommunication devices. In the near-field region, the electric and magnetic fields are decoupled and not uniform, wave impedance varies from point to point, power is transferred back and forth between the antenna and the surrounding object, and the energy distribution is a function of both the incident angle and distance from the antenna (Lin, 2007). Because the electric and magnetic fields are decoupled in the near field, the induced field can be obtained by combining the independent strengths of the electric and magnetic fields, i.e. the electric and the magnetically induced electric fields inside the body (Lin, 2007).

1.5.1 Thermal effects

The most recognized effect of RF radiation in biological systems is tissue heating. The absorption of RF-EMF energy by biological systems generates an oscillating current that is transferred into molecular motion of charged particles and water molecules, which are strongly dipolar and

are the major component of biological tissues. Polar molecules move to align themselves with the EMF to minimize the potential energy of the dipoles. Absorption and resonant oscillations in polar subgroups of macromolecules (e.g. proteins, DNA) are largely damped by collisions with surrounding water molecules. Damping or friction slows the motion of the oscillator. These collisions disperse the energy of the RF signal into random molecular motion. Tissue heating occurs because the rotational motion of molecular dipoles is hindered by the viscosity of water and interactions with other molecules, i.e. the rotational energy is transferred to the surrounding aqueous environment as heat. The magnitude of motion that results from the interaction of polar substances with electric fields is dependent on the strength and frequency of the field. In addition, the actual increase in temperature is dependent on the ability of the organism to thermoregulate. At high frequencies where the orientation of dipoles cannot keep up with the oscillations of the field, the system behaves like a non-polar substance (Stuchly, 1979).

As electrical fields penetrate complex biological tissues, the electric field is reduced as a result of dielectric constituents becoming polarized in response to the field. Standards for RF exposure of workers and the general population are based on protection against adverse effects that might occur due to increases in tissue or body temperature of 1 °C (wbSAR, ~4 W/kg) or less (after applying safety factors). Because RF-energy penetration and induced effects are dependent on the frequency of incident-field parameters and the composition of exposed tissues, quantifying SARs in small averaging regions is more relevant for evaluations of human health effects. Estimates of SARs in the head of individuals exposed to RF radiation during use of mobile phones that operate at a power output of 0.25 W indicate that the emitted energy would cause a rise in brain temperature of approximately 0.1 °C (Van Leeuwen *et al.*, 1999; Wainwright, 2000); therefore, it has been suggested it is unlikely that effects in the brain would be caused by increases in temperature (Repacholi, 2001). However, it is possible that temperature-sensitive molecular and physiological effects occur already with an increase of the temperature of ≤ 0.1 °C, while temperature changes approaching 1 °C are likely to affect several biological processes (Foster & Glaser, 2007).

Rates of temperature increase may be important in affecting a physiological change. Indeed, microwave-induced heating has been attributed to a rapid rate of heating 1–10 °C/s, which leads to acoustic waves due to expansion of tissue water. This auditory effect associated with brief pulses (1–10 μs) at frequencies of 1–10 GHz and peak power-densities of ~10^4 W/m^2 (10^3 mW/cm^2) occurs with only small increases in temperature in the head (Foster & Glaser, 2007). Low levels of exposure to RF radiation may result in small temperature changes that cause conformational changes in temperature-sensitive proteins and induce the expression of heat-shock proteins; studies on the effects of low intensity RF-EMF exposures on temperature changes and expression of heat-shock proteins are described in Section 4 of this *Monograph*.

1.5.2 Physiological effects

Non-thermal effects (or effects associated with a negligible increase in temperature) are defined as biological changes that occur with body temperature changes that are < 1 °C, below measurable heating, or in the range of thermal noise. Several arguments have been presented against the plausibility of a non-thermal mechanism by which RF radiation could affect physiological changes; these include: (a) damping effects of the water surrounding biological structures are too strong to allow resonances to exist at radiofrequencies (Adair, 2002); (b) the relaxation time – the time for a molecule to return from an excited state to equilibrium – for excitations produced

by RF fields (e.g. vibrations in molecules), is similar to the relaxation time for thermal noise, and shorter than the lifetime of the absorption and transfer of energy into resonant modes of oscillating elements in biological systems (Adair, 2003); and (c) the perturbation of the biological structure induced by the applied field must be greater than the effects of random thermal motion and the effects of other dissipative forces, such as viscous damping by the surrounding medium (Foster, 2000). Random thermal motion of charged components in biological systems (i.e. thermal noise) creates random fluctuating EMFs. Adair (2003) has concluded that it is unlikely that RF radiation with a power density of less than 10 mW/cm^2 (100 W/m^2) could have a significant effect on biological processes by non-thermal mechanisms.

Sheppard *et al.* (2008) have evaluated several potential mechanisms of interaction of RF radiation with biological systems and concluded that, other than heating and possible effects on reactions mediated by free radical pairs, RF field strengths in excess of system noise (collisions among various molecular oscillators generated largely by thermal agitation) could not alter physiological activities without also causing detectable tissue heating. Some mechanistic considerations addressed by these authors include:

- *Endogenous electric fields* involved in physiological processes (e.g. embryonic development, wound healing, and neuronal activity) have strengths in the range 1–200 V/m. While neuronal circuit oscillations were affected *in vitro* by extremely low-frequency electric fields, no mechanisms for inducing changes in cell-membrane potential at frequencies above ~10 MHz have been demonstrated. Furthermore, the net field effect on such a biological system would be the sum of the endogenous and applied fields. Thus, to alter a biological response such as ion transport through a membrane channel, the amplitude of the external signal would need to be of the same order of magnitude as the endogenous field (Adair, 2003; Sheppard *et al.*, 2008).
- *Specialized sensory systems* may be capable of detecting weak EMFs by integrating signals from numerous sensors over space and time. While specific sensory systems have been shown to exist for low-frequency, infrared and visible radiation, there is no evidence for the existence of RF-sensitive receptors in biological systems (Sheppard *et al.*, 2008). However, some sensory systems may respond to very small increases in temperature (< 0.1 °C).
- *Effects of weak RF fields that do not cause heating* would be likely to require frequency-dependent resonant absorption or multiple-photon absorption to induce an amplified signal strong enough to overcome intrinsic molecular noise (Sheppard *et al.*, 2008). This is because the photon energy of RF radiation is much smaller than thermal energy at body temperature (k•T, where k is the Boltzmann constant, 1.38×10^{-23} J/K (8.62×10^{-5} eV/K), and T is the absolute temperature), i.e. 27×10^{-3} eV per oscillating mode at body temperature. However, biological systems appear to absorb RF signals like a broadband receiver rather than eliciting line spectra characteristic of resonant vibrational motion (Prohofsky, 2004; Sheppard *et al.*, 2008). In addition, RF electric field strengths of up to 200 V/m cannot transfer sufficient energy to organelles or biological molecules to alter biological activities or affect thermal noise (kT) fluctuations, such as the opening of voltage-gated ion channels, spatial arrangements of membrane-associated ions, collision rates of charged ligands with proteins, or enzyme reaction kinetics (Adair, 2002, 2003;

Sheppard *et al.*, 2008). Adair (2002) suggested that, while coupling of RF-EMF to biological systems may exhibit resonance behaviour, damping of the vibrational motion by interactions with the aqueous environment prevents the absorption of sufficient energy to induce a biological effect. To significantly affect a biological system, the response from the RF signal must be comparable to the effect of thermal noise (Adair, 2003).

- *RF-EMF may be directed to specific sites* of a biological structure, leading to local areas of enhanced field strength. However, the smallest focal spot of concentrated energy would have a radius of the order of a wavelength, which is much larger than most cells (e.g. at 300 GHz, $\lambda = 1000$ µm). Thus, on a cellular basis, RF-energy absorption is very small. Fröhlich (1968) has suggested that incident RF energy may be captured by a large group of oscillating dipoles and integrated into a single mode of coherent vibrational energy. For this to occur and produce a coherent response, Sheppard *et al.* (2008) suggested that the energy stored in the coupled oscillators would need to be comparable to thermal energy and protected from damping by water or other molecules. In addition, energy and thermal diffusion prevent the formation of significant temperature differences at the cellular and subcellular levels.
- *In order for RF electric fields to induce small changes in protein structure* that would affect binding of substrates or ligands to enzymes or receptor proteins, extremely high field strengths would be required (~10^9 V/m) (Sheppard *et al.*, 2008).

Since living systems are not in thermal equilibrium, mechanistic theories on interactions between RF-EMF and biological tissues must consider the non-equilibrium and nonlinearity of these systems. Binhi & Rubin (2007) suggest that biochemical effects may be induced by weak EMFs in targeted systems that are in non-equilibrium states in which the time to transition from an intermediate metastable state to a final active or inactive state may be less than the thermalization time of the induced field.

Prohofsky (2004) has suggested that protein conformation might be affected by RF radiation if amplitudes of specific vibrational modes were altered. However, only intermolecular vibrational modes of proteins and the surrounding tissue are possible at RF frequencies, because high-frequency intramolecular resonant vibrational modes exist above several hundred GHz. Further, this author concluded that the biological effects of RF radiation in macromolecules (proteins and DNA) can only be due to temperature changes, because the absorbed energy associated with intermolecular vibrations is rapidly thermalized; the relaxation time for coupling RF waves to surrounding water (i.e. damping) is faster than the speed with which it can be transferred to intramolecular resonant modes. A non-thermal effect might exist if there were a very strong energy coupling between the intermolecular and intramolecular modes. Exceptions to the above-mentioned considerations are proteins such as myoglobin or haemoglobin, in which the haem group can oscillate in the protein pocket at lower frequencies (184 GHz is the lowest mode in myoglobin) (Prohofsky, 2004).

Any theories on the potential effects on biological systems of RF energy at low field strengths must account for the facts that biological systems do not exist at equilibrium, that the dynamic nature of these systems is controlled by enzyme-mediated reactions, and that primary effects may be amplified by nonlinear biological processes (Georgiou, 2010). The reproducibility of reported effects may be influenced by exposure characteristics (including SAR or power density, duration of exposure, carrier frequency, type of modulation, polarization, continuous versus

intermittent exposures, pulsed-field variables, and background electromagnetic environment), biological parameters (including cell type, growth phase, cell density, sex, and age) and environmental conditions (including culture medium, aeration, and antioxidant levels) (Belyaev, 2010).

A biophysical theory on how low-intensity RF-EMF exposures might affect physiological functions involves the alteration of ligand binding to hydrophobic sites in receptor proteins (Chiabrera *et al.*, 2000). Collisions of the ligand ion in the hydrophobic region of the receptor protein result in loss of its vibrational energy. In order for RF exposures to affect the binding probability of an ion ligand with a membrane protein receptor, basal metabolic energy would have to amplify the effect of the RF field by maintaining the cell in thermodynamic non-equilibrium. Otherwise, the low-intensity exposure would be negligible compared with thermal noise. Other elements of this model that were used to evaluate the effects of low-intensity RF exposures on ligand binding are the extremely fast ("instantaneous") rearrangement of atoms in the hydrophobic core of protein by the ligand ion, the fact that the endogenous field at the protein boundaries is large enough to exclude water molecules from the hydrophobic core, and that the ion-collision frequency near the hydrophobic binding site is much less than it is in water. The authors of this study noted that thermal noise must be taken into account when evaluating potential biological effects of RF exposures (Chiabrera *et al.*, 2000).

Demodulation of pulsed RF signals (e.g. GSM pulsed at 217 Hz) might produce low-frequency electric fields (Challis, 2005). To confirm a biological effect from a low-frequency, amplitude-modulated RF signal, a nonlinear response in the biological sample would be expected (Balzano & Sheppard, 2003). Except for the case of an incident flux of RF energy at extremely high field-strength pulses that causes mechanical vibrations, most oscillators in a biological system respond linearly to the incident low-energy photons in the RF spectrum; the dispersion of RF energy into random molecular motion energy occurs without generating harmonics of the incident signal in the energy spectrum of re-radiated photons by the exposed material. However, the authors of this study considered the possibility that demodulation of high-frequency incident RF signals might produce nonlinear interactions with biochemically induced transient oscillators in living tissues (e.g. uncoupled electrons of free radicals) by extracting low-energy signals. If this occurred, then the spectrum of RF-emission energy emitted from the exposed tissue would be altered, producing a second harmonic that would show up as a spectral line at twice the frequency of the incident signal (Balzano & Sheppard, 2003). Sensitive, frequency-selective instruments are available to detect the presence of frequency-doubling signals produced by nonlinear interactions between amplitude-modulated RF signals and molecular oscillators vibrating in unison in living cells (Balzano, 2003). Exposure of several different types of cell and tissue to continuous wave fields (input powers of 0.1 or 1 mW) in a double-resonant cavity at the resonant frequency of the loaded cavity for each sample (~880–890 MHz) did not emit second harmonic signals at twice the frequency of the incident signal (Kowalczuk *et al.*, 2010). SAR values were approximately 11 mW/g for cells and 2.5 mW/g for tissues exposed to 1 mW RF fields. Although these results were inconsistent with the hypothesis that living cells can act as effective radio receivers and demodulate RF energy, a second harmonic response may be elicited by much more intense continuous waves (which would be likely to cause rapid heating) or very short-pulsed RF signals (Kowalczuk *et al.*, 2010). Sheppard *et al.* (2008) concluded that it is unlikely that modulated RF fields significantly affect physiological activities of membranes, because non-thermal stimulation of cell membranes has not been observed above approximately 10 MHz and the voltage across a cell membrane from an

amplitude-modulated RF electric field of 100 V/m is much lower than the low-frequency voltage noise associated with membrane voltage fluctuations. Much higher incident field strengths, at levels that would cause significant tissue heating, would be needed to create electric fields comparable with endogenous fields.

Lipid–protein complexes appear to be more sensitive to perturbations from RF radiation at membrane phase-transition temperatures (Liburdy & Penn, 1984; Allis & Sinha-Robinson, 1987). Blackman *et al.* (1989) suggested that the chick brain surface is also poised at a phase transition at physiological temperatures, and the long-range order that occurs in such a state would minimize the thermal noise limitations calculated for single-phase systems on signal detection of weak RF radiation. Consistent with this hypothesis, Blackman *et al.* (1991) observed that RF radiation-induced calcium-ion efflux-changes occurred only within the narrow temperature range of 36–37 °C.

The aggregation of dielectric objects by attractive forces between them is referred to as the pearl-chain effect (Challis, 2005). RF fields of about 125 V/m and at frequencies of up to about 100 MHz can produce oscillating fields in cells that enhance their attraction. At higher frequencies the induced dipoles might not have sufficient time to reverse direction and, therefore, stronger fields would be needed to produce the same attractive energy.

Electroporation is a process by which short pulses (~100 μs) of strong electric fields (e.g. 10–100 kV/m) are applied to cell membranes to induce transient pores that allow uptake of drugs, DNA, or other membrane-impermeable substances (Foster, 2000; Sheppard *et al.*, 2008). These changes occur without causing significant tissue heating or thermal damage.

1.5.3 Magnetic-field effects

Low-frequency magnetic fields might produce biological effects if they induce ferromagnetic resonance in tissues that contain high concentrations of iron particles (magnetite) (Challis, 2005).

Free radicals, which are highly reactive molecules or ions with unpaired electrons, are formed when radical pairs dissociate. By altering the recombination of short-lived radical pairs with antiparallel spins, low-intensity magnetic fields may increase the concentration of free radicals (Challis, 2005; Georgiou, 2010). The expected increase in radical concentration is 30% or less (Timmel *et al.*, 1998). The extent to which this increase can produce oxidative stress-induced tissue damage (e.g. membrane-lipid peroxidation or DNA damage) is not known. Furthermore, radicals are also a part of normal cellular physiology, being involved in intracellular signal transduction (Finkel, 2003). Therefore, even small effects on radical concentration could potentially affect multiple biological functions. By prolonging the lifetime of free radicals, RF fields can increase the probability of free-radical-induced biological damage. To affect DNA recombination and thus the repair of damage caused by radicals, external magnetic fields must act over the times that the radical pairs dissociate ($> 10^{-9}$ s); hence, Adair (2003) concludes that the effect of RF fields on free-radical concentrations would likely be limited to about 10 MHz or less. Resonance phenomena occur below 10 MHz, and may result in biological effects from low-level RF fields at about 1 MHz (Henbest *et al.*, 2004; Ritz *et al.*, 2009).

Georgiou (2010) cited several studies that provide evidence for the induction of oxidative stress via the free-radical pair mechanism in biological systems exposed to RF radiation; some of the reported effects include increased production of reactive oxygen species, enhancement of oxidative stress-related metabolic processes, an increase in DNA single-strand breaks, increased

lipid peroxidation, and alterations in the activities of enzymes associated with antioxidative defence. Furthermore, many of the changes observed in RF-exposed cells were prevented by (pre)treatment with antioxidants.

1.5.4 Conclusion

In conclusion, tissue heating is the best-established mechanism for RF radiation-induced effects in biological systems. However, there are also numerous reports of specific biological effects from modulated RF-EMF, particularly low-frequency modulated fields (see Section 4). Mechanistic studies will be needed to determine how effects that are reproducible might be occurring, e.g. via the induction of reactive oxygen species, induction of ferromagnetic resonance, demodulation of pulsed RF signals, or alteration of ligand binding to hydrophobic sites in receptor proteins. Although it has been argued that RF radiation cannot induce physiological effects at exposure intensities that do not cause an increase in tissue temperature, it is likely that not all mechanisms of interaction between weak RF-EMF (with the various signal modulations used in wireless communications) and biological structures have been discovered or fully characterized. Biological systems are complex and factors such as metabolic activity, growth phase, cell density, and antioxidant level might alter the potential effects of RF radiation. Alternative mechanisms will need to be considered and explored to explain consistently observed RF-dependent changes in controlled studies of biological exposure (see Section 4 for examples of reported biological effects). While the debate continues on whether or not non-thermal biological effects occur as a result of exposures to low-intensity RF radiation, it may be difficult to specify observed effects as non-thermal because of the high sensitivities of certain physiological responses to small increases in temperature.

1.6 Exposure to RF radiation

Exposure of workers and the general community to RF radiation can occur from many different sources and in a wide variety of circumstances. These exposures can be grouped into three major categories: personal, occupational and environmental.

1.6.1 Personal exposure

The general community can come into contact with several potentially important sources of RF radiation as part of their personal life, involving some degree of choice, including use of a mobile phone, other communication technologies, or household devices (see Section 1.2).

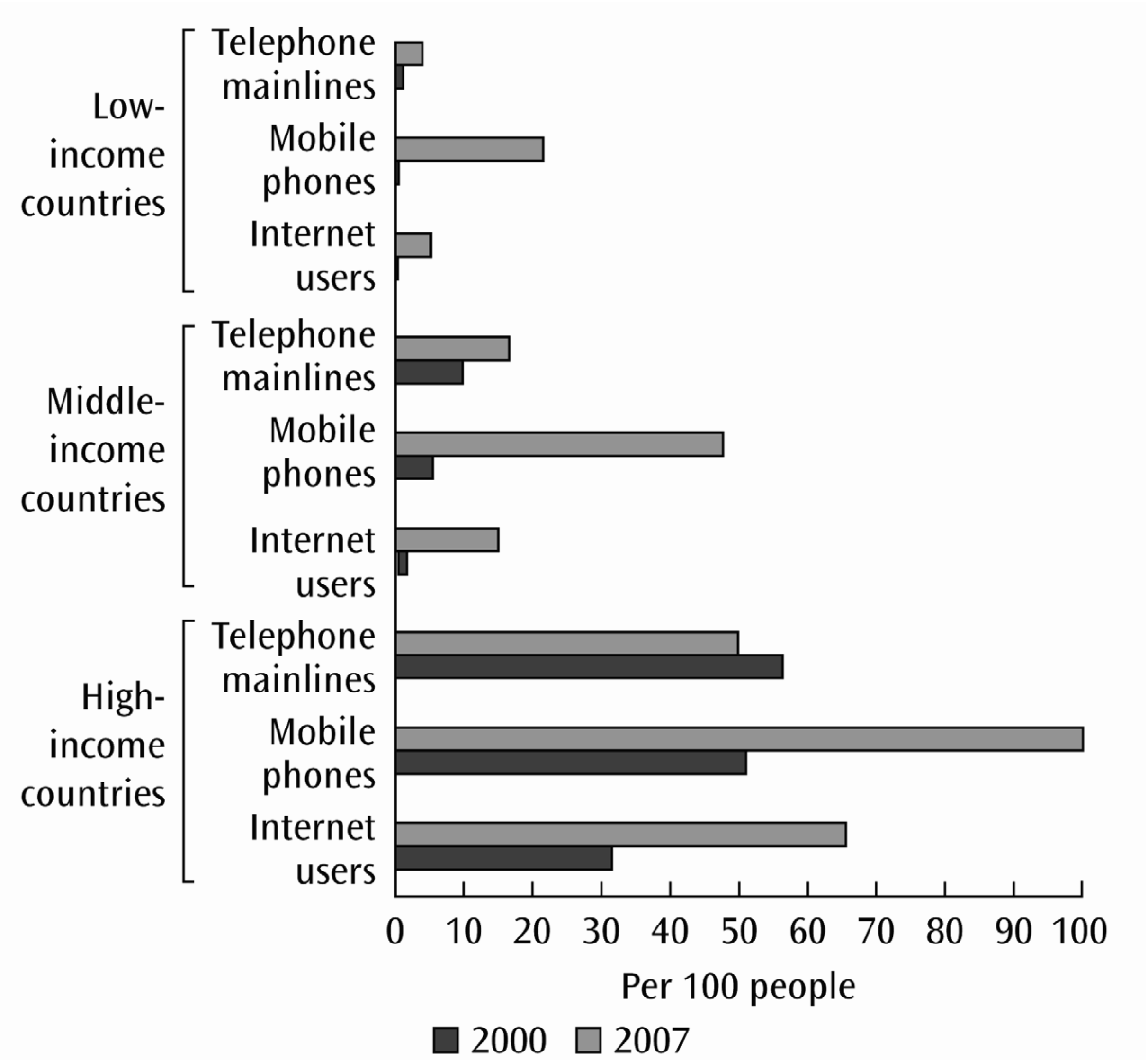
(a) Mobile phones

(i) Increase in mobile-phone subscriptions

Analogue mobile phones were first introduced around 1980 and GSM phones in the mid-1990s. Over the past two decades, the number of people owning a mobile phone has increased rapidly around the world. For example, the number of mobile-phone subscribers in the USA has risen from 0.34 million in 1985 to 109 million in 2000, and 263 million in 2008 (InfoPlease, 2011). WHO has estimated that at the end of 2009 there were 4.6 billion mobile-phone subscriptions globally (WHO, 2010b). Fig 1.17 illustrates the rapid rise in mobile-phone subscriptions compared with other types of phone and Internet usage over the past decade, although it should be noted that the number of subscriptions does not equate to number of users, as some people have more than one subscription and a single subscription can be used by more than one person.

This rapid increase in mobile-phone use is not just restricted to the industrialized countries. Fig 1.17 shows the increase in mobile-phone subscriptions from 2000 to 2007 in high-, middle- and low-income countries (World Bank, 2009). While industrialized countries continue to

Fig. 1.17 Mobile-phone subscriptions per 100 people in high-, middle-, and low-income countries, 2000 and 2007



From World Bank; International Monetary Fund (2009)

have the highest number of subscriptions per 100 people, the percentage increase over this time has been much greater in low- and middle-income countries. In low-income countries, subscription rates in 2000 were negligible, but in 2007 they were 25% of the rate in high-income countries, while in middle-income countries the rise was from about 10 to 50 subscriptions per 100 people, to reach about 50% of the rate in high-income countries in 2007.

There have also been considerable changes in the types of mobile phone used over the past 10 years, which has important implications for RF exposure of the user (see Section 1.2). Earlier mobile phones used analogue technology, which emitted waves of 450–900 MHz. Digital phones, with RF frequencies of up to 2200 MHz, were introduced in the mid-1990s and by the year 2000 had almost completely replaced analogue phones. The largest growth in recent years has been for smartphones, which allow the user access to a wide range of non-voice data applications (taking photographs, Internet access, playing games, music, and recording videos). In the USA, 18% of phones in 2010 were smartphones, up from 13% in 2008 (Nielsen, 2010).

(ii) Mobile-phone use among children

Within the increasing subscription figures, there have been questions raised about increasing use of mobile phones by children. As was seen in Section 1.3, published dosimetry studies using phantom heads have found that RF absorption can be higher in children than in adults, due to anatomical and physiological differences. A recent study used a modified version of the Interphone questionnaire in 317 children in secondary school (median age, 13 years) in one state of Australia, and found that 80% used a mobile phone (Redmayne *et al.*, 2010). Data on national use of mobile phones in 2009, collected by the Australian Bureau of Statistics (ABS), has shown that 31% of Australian children had a mobile phone, with the highest ownership being in the age group 12–14 years (76%) (ABS, 2009). Similar rates of mobile-phone use by children were found in three major cities in Hungary in 2005, where 76% of children in secondary school owned a mobile phone, 24% used a mobile phone daily to make calls, and an additional 33% used mobile phones to make calls calls at least several times per week (Mezei *et al.*, 2007).

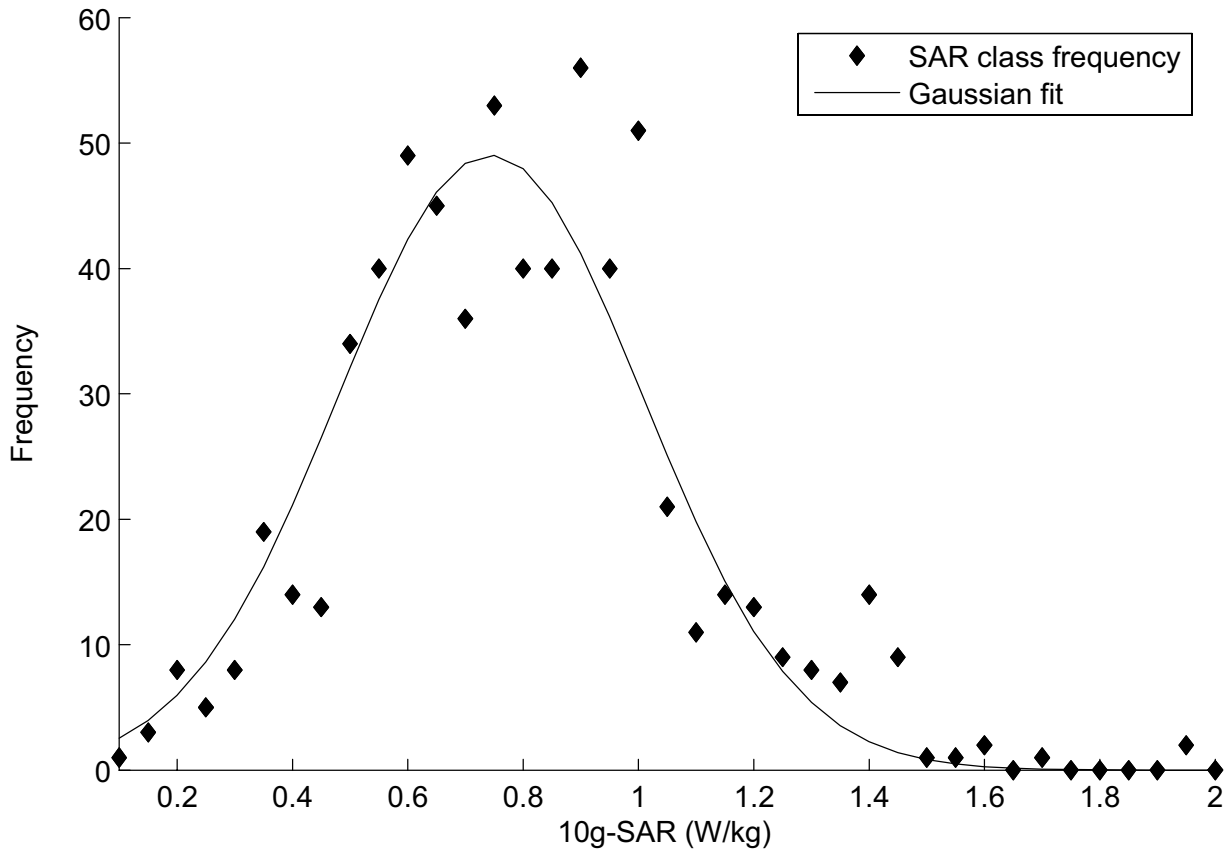
While the increase in mobile-phone subscriptions over the past 15 years is well documented, less is known about changes in call frequency and duration over that time. One study in Finland found that the median duration of calls per month was 186 minutes in 2007, increasing to 221 minutes in 2009, while the average monthly number of calls increased slightly from 52 to 57 calls (Heinävaara *et al.*, 2011). The daily local RF exposure of the general public has increased by several orders of magnitude with the introduction and proliferation of mobile handsets. This has triggered concern among health agencies and the public, since the tissue with the highest exposure is the brain. Figs 1.18 and 1.19 display the frequency of worst-case SAR from mobile phones, measured according to IEEE (2003) and CENELEC (2001) guidelines.

Fig. 1.18 represents the typical SAR values for Europe (mean psSAR-10 g, 0.74) and Fig. 1.19 for North America (mean psSAR-1 g, 0.96). The different averaging masses are due to different legal regulations in Europe and the USA. These values are a considerable percentage of the limit values (see Section 1.7). A recent statistical analysis of the SAR database of the Federal Communications Commission (FCC) found that the SAR values of newer phones are typically lower than those of older phones, despite the greatly reduced size (see Section 1.3).

(iii) Exposure metrics for epidemiological studies

To develop suitable exposure metrics for use in epidemiological studies on RF exposure from mobile phones and health effects such as cancer, there is a need to access technical data such as

Fig. 1.18 Statistical distribution of maximum psSAR-10 g measured for 668 mobile phones, according to standard EN50361 (CENELEC, 2001)

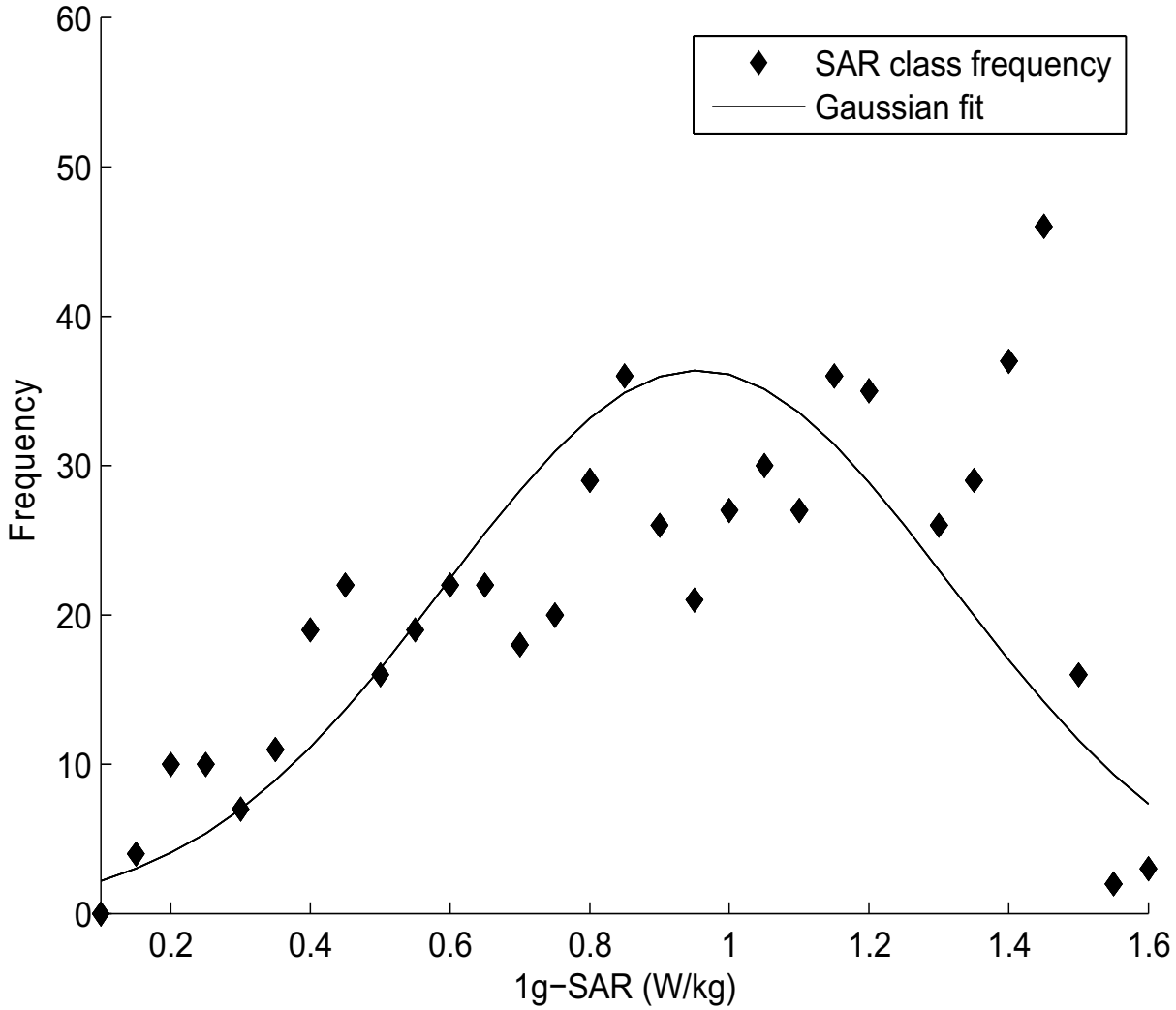


Data from German Federal Office for Radiation Protection, in Kühn & Kuster (2007)

the generation of phone, frequency, modulation and network-related factors that might influence the output power of the phone, as well as reliable information about the pattern of mobile-phone use from each subject. This includes such variables as reported number of calls, duration of calls and laterality, i.e. the side of the head on which the phone is most often placed by the subject when talking on the phone.

As exposure data related to mobile-phone use are usually collected from the subjects themselves, several studies have been conducted to test the validity of this type of self-reported information. Several methods are available to validate self-report, including telephone-company records, software-modified phones and hardware-modified phones (Inyang *et al.*, 2008). A study of 59 children in the seventh year of school (age 11–12 years) in Australia used GSM-type software-modified phones to record exposure details (e.g. number and duration of calls) to validate questionnaire data on mobile-phone use. This study found a modest correlation of 0.3 for recall of number of calls, but almost no correlation (0.1) for duration (Inyang *et al.*, 2009). There was little difference with the main findings for different demographic groups, although for some subgroups, numbers were small. This study was carried out over one week and a possible explanation of the poor correlations is that the change in phone type imposed by the study protocol (from 3G to GSM) may have

Fig. 1.19 Statistical distribution of maximum psSAR-1 g measured for 687 mobile phones, according to standard IEEE-1528 (CENELEC, 2001)



Data from Federal Communications Commission, in Kühn & Kuster (2007)

resulted in a change in phone-use behaviour for many of the children.

Another potential problem is differential recall of mobile-phone use in case–control studies. In the CEFALO case–control study of brain tumours in adolescents, a validation study was undertaken to estimate the effect of both random and systematic errors in 59 cases (26% of all cases who owned a mobile phone) and 91 controls (22% of all controls who owned a mobile phone) for whom phone-use data were available from the mobile-phone provider (Aydin *et al.*, 2011). The study found that cases overestimated their number of calls by 9% on average, and controls overestimated by 34% on average. Cases also overestimated the duration of their calls by 52% on average, while controls overestimated by a much greater 163%, suggesting that duration-of-call data from self-reports are less reliable and may be more prone to recall bias than self-reports of number of calls in studies of cancer in children.

Such differential reporting between cases and controls was not such a problem in two validation studies undertaken as part of the Interphone case–control study of brain tumours in adults. A 6-month volunteer study used the Interphone questionnaire and either phone records or software-modified phones in 11 countries and found that, although there was considerable random error, there was fair to moderate agreement for both number and duration of calls, with weighted kappas ranging from 0.20 to 0.60 (Vrijheid *et al.*, 2006). In addition, there was some systematic error, as heavy users tended to overestimate their use, while lighter users tended to underestimate theirs. There was also some heterogeneity between countries. A subsequent validation study among subjects from five countries in the Interphone study compared reported mobile-phone use against phone records over an average of two years. This substudy found that the extent of underreporting of number of calls (0.8) and of over-reporting of call duration (1.4) was similar in each group. Differential recall was greater with longer periods of recall, although numbers were small for the group with longest recall period (Vrijheid *et al.*, 2009b). More recently, a pilot study in Finland for the prospective cohort study of mobile-phone users (COSMOS study) validated reported phone use against phone-company records for 418 subjects who had a single operator (Heinävaara *et al.*, 2011). The authors found that overestimation of reported mobile-phone use was common and there was moderate agreement (kappa = 0.60) for monthly average duration of calls, although there was more overestimation and less agreement as the call duration increased. A further small validation study in 60 engineers and scientists, who are not representative of the wider community, used mobile-phone records to validate self-reporting and found similar agreement; the conclusion was, that reporting monthly use was more reliable than weekly or daily use (Shum *et al.*, 2011).

Laterality, i.e. against which ear the mobile phone is mainly held during calls, is another important factor that can influence estimations of exposure within the head. Laterality does not always coincide with the subject's dominant hand and may be related to other activities, such as writing. A validation study of self-reported laterality with hardware-modified phones found that agreement between the information from these phones and self-reported laterality was modest, with a kappa of only 0.3 (Inyang *et al.*, 2010). Schüz (2009) demonstrated that laterality effects are similar across exposure categories and highlighted the problem of possible reporting bias. The Interphone study has addressed this problem in a sensitivity analysis, whereby different allocations of side-of-head were used; this caused only minor reductions in the odds ratios for the highest quintile of exposure, which suggests that the findings are not sensitive to errors in the recall of laterality of phone use (Cardis *et al.*, 2011a).

Mobile phones are low-powered RF transmitters, operating at frequencies between 450 and 2700 MHz, with peak powers in the range of 0.1 to 2 W, the power being highest during a call. The handset only transmits RF power when it is turned on, but the newer smartphones regularly give short bursts of power to check e-mails and other Internet services. One study has found that mobile-phone output power is usually higher in rural areas where base stations are further apart, whereas the other factors examined in the study (length of call, moving/stationary, indoor/outdoor) were found to be of less importance as predictors of power output from the phone (Hillert *et al.*, 2006).

Using a mobile phone in areas of good reception (such as in cities where mobile phone-base stations are close together) also decreases exposure as it allows the phone to transmit at reduced power. Conversely, people using a phone in rural areas where mobile-phone reception is poorer may receive higher RF exposure. This was one

factor examined in a study of 512 subjects in 12 countries who were asked to use GSM software-modified phones; the study, monitored date, time and duration of each call, frequency band and power output for a month (Vrijheid *et al.*, 2009a). The main predictors of power output were the study location, the network, and the duration of the call, with shorter calls being associated with higher power output. The measured power levels in GSM networks were substantially higher than the average levels theoretically achievable, which has important implications for estimating exposure in epidemiological studies. Rural location was only a major factor in Sweden, where subjects were living in very sparsely populated areas; these results are consistent with those of an earlier paper from Lönn *et al.* (2004) in Sweden, who reported that the highest power level was used about 50% of the time in the rural areas, but only about 25% of the time in urban areas. This highlights the problem of identifying genuinely sparsely populated rural areas where major differences in power output can be found. Another paper from the Interphone study reported an investigation of the effects of parameters that were thought to influence the level of RF SAR in the brain. Total cumulative specific energy was estimated, based on data collected during the Interphone study, to assess the relative importance of the different factors and these results were used to develop an algorithm, which was tested on study subjects in five countries (Cardis *et al.*, 2011b). This study found that the type of phone with the highest mean total specific cumulative energy (TSCE) was AMPS800 (5165 J/kg), followed by D-AMPS800 (3946 J/kg), GSM800/900 (2452 J/kg), GSM1800 (4675 J/kg), CDMA1900 (1855 J/kg), and CDMA800 (164 J/kg). The main determinants were communication system, frequency band, and number and duration of mobile-phone calls. The study also identified several uncertainties in relation to SAR estimation, including those related to spatial SAR distribution for each phone class, error in recall of phone use, and laterality and uncertainties about the most biologically relevant dose metric.

A study in the USA examined the impact of phone type and location by use of software-modified phones driven over several pre-determined routes (Kelsh *et al.*, 2010). This study found that RF levels were highest for the older analogue phones, intermediate for GSM and TDMA phones, and lowest for CDMA phones. The main predictors of RF level were phone technology and, to a lesser extent, degree of urbanization.

Patterns of personal mobile-phone use have been changing as technology has changed and this can have implications for the strength of the RF field experienced by the user. One important development has been the introduction of the short message service (SMS), which was originally designed for GSM to allow sending non-voice text messages (Herring, 2004). SMS was first introduced in 1993, but use increased rapidly in the mid-2000s. Text messaging using SMS leads to lower RF exposure than voice calls in two ways: the phone is usually held at least 30 cm from the body during the writing and sending of an SMS and the duration of power output is much shorter (about 11 seconds) than the duration of a voice call.

As with SMS, other mobile-phone communication innovations have been developed that result in lower potential for SAR exposure than voice calls. A person using a mobile phone at least 30 cm away from the body, e.g. when accessing the Internet, with a hands-free device for voice calls or "push-to-talk" with the phone held in front of the head, will therefore have a much lower exposure to RF than someone holding the handset against the head during a voice call.

(b) DECT phones

Another important source of personal RF exposure is the home use of DECT phones, which have been replacing traditional handsets in the home. As the DECT base-station is within

the home and at most some tens of metres from the handset, the average power generated by the DECT phone is less than that of a mobile phone, where the base station may be up to some kilometres away. However, the power output of a DECT base station in close proximity to a person may be comparable to that of a 3G phone, so proximity to a DECT phone base-station should be taken into account when estimating RF exposure in epidemiological studies in which sizeable numbers of subjects have used 3G phones. A recent study of Australian schoolchildren found that 87% had a DECT phone at home, and although there was only a weak correlation (r = 0.38) between mobile-phone and DECT-phone use, this suggests that DECT-phone use needs to be considered in the assessment of RF exposure (Redmayne *et al.*, 2010).

(c) Other communication technologies and domestic sources

The incident-field exposures from typical devices used in home and office environments have been assessed (Kühn *et al.*, 2007a). The maximum E-field exposure values for different device categories are summarized in Table 1.13. The incident-field exposure from cellular base stations may be exceeded by the exposure from these devices due to the generally closer distances involved.

Additionally, an incident exposure of 1 V/m translates to a psSAR value in the brain that is approximately 10 000 times lower than the maximum exposure from a handset. Thus, handsets are by far the most dominant source of RF exposure for the general population.

Within homes there are many other potential sources of RF exposure, including baby monitors, microwave ovens, Wi-Fi, Bluetooth, various types of radios and remote-controlled toys. A study of 226 households in lower Austria measured the peak power of emitted bursts of RF exposure from each of these types of devices in bedrooms, where the residents spend the most time in one position. The highest peak RF values were measured for mobile-phone and DECT base stations in the 2400-MHz band (Tomitsch *et al.*, 2010).

Table 1.13 Worst-case E field at distances of 20 cm and 1 m from typical wireless indoor devices

Device class	Frequency range (MHz)	Worst-case E field (V/m)	
		20 cm	1 m
Baby surveillance	40 – 863	8.5	3.2
DECT	1880 – 1900	11.5	2.9
WLAN	2400 – 2484	3.9	1.1
Bluetooth	2402 – 2480	3.1	1.0
PC peripherals	27 – 40	≤ 1.5	≤ 1.5

DECT, digital enhanced cordless telecommunications; PC, personal computer; WLAN, wireless local area network
Adapted from Kühn *et al.* (2007a)

1.6.2 Occupational exposure

There are many occupations involving potential sources of exposure to RF radiation in the workplace, the more important of which involve work with high-frequency dielectric heaters (PVC welding machines) and induction heaters, broadcast sources, high-power pulsed radars, and medical applications including MRI and diathermy.

(a) High-frequency dielectric heaters and induction heaters

High-frequency dielectric heaters (PVC welding machines) functioning at 27 MHz have traditionally involved the highest occupational exposures to RF (Allen, 1999). This is not a large sector of the industrial workforce, although it is estimated that there are about 1000–2000 PVC dielectric welders in Finland, which has a total population of about five million people. The whole-body average SAR for dielectric heater operators has been estimated to vary from 0.12 to

2 W/kg and it is not uncommon for these workers to report heating effects (Jokela & Puranen, 1999).

(b) Broadcasting sources

The rapid increase in mobile-phone use and other communication technologies worldwide has required increasing numbers of workers to undertake monitoring and maintenance. A study of exposure to RF radiation from two medium-sized antenna towers in Finland was conducted to document worker exposure (Alanko & Hietanen, 2007). These towers contained transmitting antennae of several different types, mobile-phone networks (GSM900 and GSM1800), radio and digital television substations and other radio systems. Although the measured power density was quite variable, the maximum instantaneous power density at this site was 2.3 W/m^2, which was recorded during maintenance tasks at the tower with the GSM1800 antennae. For the tower with both GSM900 and GSM1800 antennae, the maximum registered instantaneous power density inside the climbing space was 0.4 W/m^2. [The Working Group agreed with the authors who concluded that exposures will depend on the different types of antennae located on the towers and that it is usually difficult to predict occupational RF exposures.]

The above approach to assess exposure is based on spot measurements and does not give an estimate of cumulative exposure over working time, which is the approach employed with other types of workplace hazards. Attempts have been made to employ this cumulative dose approach for exposure to RF radiation, but as there are usually many different sources of RF radiation present in a workplace, this is not straightforward. For example, such an approach was used to assess total exposure and estimate an annual dose on fast patrol boats in the Norwegian Navy, which carry high-frequency antennae and radar (Baste *et al.*, 2010). This study found considerable variation in exposure at different points around the boats, the highest exposures and annual dose being found in the captain's cabin. These estimates were done for three time periods (1950–79, 1980–94 and 1995+), and relied on recall of transmission characteristics over several decades. The estimated annual doses in the most recent period were about one third of those in the earliest period. The estimated annual doses for the period from 1995 and later ranged between 4.3 and 51 kVh/m.

(c) Other potential sources of radiofrequency radiation in the workplace

Portable radios, short-wave and surgical diathermy are other potential sources of RF radiation in the workplace, whereas base stations, microwave links and microwave ovens have been considered unlikely to give rise to substantial exposures (Allen, 1999). For example, a study of exposure to RF radiation in police officers operating speed guns (measurements made at the seated ocular and testicular positions) found that almost all of the 986 measurements made for 54 radar units were below the detection limit, the highest power-density reading being 0.034 mW/cm^2 (Fink *et al.*, 1999).

1.6.3 Environmental exposure

The most common sources of RF in the general environment are mobile-phone base stations, which tend to be operated at the lowest power possible for reasons of network efficiency (see Section 1.2; Allen, 1999). The level of RF exposure is usually poorly correlated with proximity to the antenna, although there is considerable variation in output power from site to site (Section 1.2). A study regarding indoor incident-field exposure from cellular base-station sites was conducted by Austrian Research Centers (ARCS) in the city of Salzburg, Austria (Coray *et al.*, 2002). Table 1.14 shows two cumulative incident-field exposure values (sum of incident-field exposure from multiple transmitters at one site) measured at different distances from several base-station

Table 1.14 Measurement of indoor incident electric-field (E) strength at base stations in Salzburg, Austria[a]

Base station	Measurement 1		Measurement 2	
	Distance to base station (m)	Cumulative incident E field (V/m)	Distance to base station (m)	Cumulative incident E field (V/m)
1	196	0.37	347	0.35
2	88	0.51	108	0.89
3	9	0.034	15	0.037
4	16	0.62	8	1.00
5	85	0.94	152	0.75
6	81	1.8	85	1.71
7	4	3.9	25	1.02
8	93	0.19	208	0.19
9	34	0.40	55	0.63
10	39	1.9	76	2.8
11	174	0.59	220	0.45
12	41	0.70	107	0.67
13	2.5	0.25	5.5	0.15

[a] For each base station site, two examples of measurements of cumulative incident field exposure (sum of incident field exposure from multiple transmitters at one site) at different distances are shown.
Compiled by the Working Group from BAKOM Report, Coray *et al.* (2002)

sites. The values are between 0.1 and 1 V/m for distances of up to several hundreds of metres. Values greater than 1 V/m and up to 3.9 V/m were measured for distances of less than 86 m. These data also underline that the distance to the base station site has a poor correlation for the incident exposure. Similar results were reported in a study that also included outdoor measurement points and addressed the time dependence, i.e. traffic dependence of the exposure from cellular base stations. The results showed a substantial time dependence for base stations with multiple traffic channels. In these cases, clearly lower exposure can be expected at night and at weekends (Bornkessel *et al.*, 2007).

In an attempt to measure typical exposure to RF radiation over a whole week, volunteers in a Swiss study were asked to wear an RF exposimeter and to complete an activity diary (Frei *et al.*, 2009b). The main contributions to exposure were found to come from mobile-phone base stations (32.0%), mobile-phone handsets (29.1%) and DECT phones (22.7%).

Breckenkamp *et al.* undertook a validation study of exposure to RF radiation in 1132 households in Germany located within 500 m of at least one mobile-phone base station (average number of base stations, 3.4; average number of antennae, 17) (Breckenkamp *et al.*, 2008). An exposure model was developed, based on 15 parameters related to the base station and the antennae, from the database of the federal network agency and information about the home from the residents and interviewer. Dosimetric measurements were undertaken in the bedroom of the home in 2006. There was considerable variability across cities (range of kappa values, 0.04–0.49), with higher kappa related to low-density housing with buildings comprising more than three floors. There was greater agreement for households located less than 300 m from the base stations and the authors concluded that the model was only useful where high-precision input data were available.

Little is known about geographical variation in exposures in different settings in the general community, but published data related

to exposures within different forms of transport, homes, offices and outdoors in five European countries were reviewed in a recent study (Joseph *et al.*, 2010). Power density (mW/m^2) was measured in each microenvironment and highest exposures were measured in transportation, followed by outdoor environments, offices and homes. In the Netherlands, the highest exposures were measured in the office environment. In all studies, the lowest exposures were in the home, with exposures of about 0.1 mW/m^2 recorded in all countries. In transport vehicles, virtually of the exposure was from mobile phones, whereas in offices and homes, the sources were quite variable between countries. [The Working Group suggested that these conclusions should be treated with some caution, as it was not clear how representative the measured microenvironments were.]

In a feasibility study in Germany, the aim of which was to develop reliable exposure metrics for studies of health effects of exposure to RF radiation from mobile-phone base stations, data were collected on distance to base station and spot measurements at the homes of nine controls taking part in a case–control study of cancer. Distance from base station was a poor proxy for the total power density within the home due to the directional characteristics of the base-station beam, scattering, shielding and reflection of the radiated fields and the contribution to power density from other sources (Schüz & Mann, 2000). [The Working Group noted that use of this metric would be likely to result in considerable exposure misclassification.]

A further study of a random sample of 200 subjects in France used a personal exposure meter to estimate the doses, time patterns and frequencies of RF exposures with measurements of electric-field strength in 12 different bands at regular intervals over 24 hours (Viel *et al.*, 2009). This allowed differentiation of different sources of RF radiation, including mobile-phone base stations. For each of GSM, DCS and UMTS, more than 96% of the measurements were below the detection limit and the median of the maximum levels for all three systems ranged between 0.05 and 0.07 V/m. In addition, exposures were found to vary greatly at similar distances from GSM and DCS base stations, although two peaks were observed (at 280 m mainly in urban areas, and 1000 m mainly in periurban areas), although most distances exceeded the 300 m within which the exposure model developed by Breckenkamp *et al.* (2008) was found to have the highest agreement with measured levels.

In another study by Frei *et al.* (2009a), the aim was to develop a model to predict personal exposure to RF radiation. One hundred and sixty-six subjects carried a personal dosimeter for one week and completed a diary. Important predictors of exposure were housing characteristics, ownership of communication devices, time spent in public transport, and other behavioural aspects, with about half of the variance being explained by these factors.

A range of personal exposure meters is now available. These are more robust for the purposes of exposure assessment in epidemiological studies, and a considerable step forward compared with the traditional spot-measurement approach, which is usually chosen for compliance purposes and does not result in a representative estimate of personal exposure (Mann, 2010). [The Working Group noted that care needs to be taken in interpreting the results of personal exposure measurements, because of the low sensitivity and the failure to account for the fact that they respond to TDMA signals, which may lead to an overemphasis of DECT, Wi-Fi and GSM phone signals in average exposure. Because burst powers may have been measured for these signals, rather than average powers, any exposure proportions attributed to source categories in these studies should be treated with caution when assessing exposure for epidemiological studies.]

1.7 Exposure guidelines and standards

Guidelines and standards for limiting human exposure to RF fields have been developed by several organizations, the most prominent being those of the International Commission on Non-Ionizing Radiation (ICNIRP) and the Institute of Electrical and Electronic Engineers (IEEE). ICNIRP published its present RF guidelines in 1998 (ICNIRP, 1998) and restated them in 2009 (ICNIRP, 2009a). IEEE published its present guidelines in 2005 (IEEE, 2005), but its 1999 guidelines are still used in some countries (IEEE, 1999).

These guidelines contain restrictions on exposure that are intended to assist those with responsibility for the safety of the general public and workers. The guidelines provide clearly defined exposure levels below which the established acute health effects of exposure are avoided. Exposures can be measured or calculated and compared with these values. If exposures are found to be above the guideline values, measures are put in place to reduce exposure. The guidelines apply to all human exposures to EMFs, irrespective of how such exposures arise, and they do not make specific mention of sources.

The guidelines are not mandatory by themselves, but have been adopted by regulatory authorities and governments in many countries/regions of the world in a variety of different ways. Some regulatory regimes focus on limiting exposures of the public and/or workers, while others focus on limiting product emissions (to control exposures) as part of the certification process before placing products on the market. For example, harmonized technical standards have been implemented in Europe that provide a basis for assessing exposures from equipment such as mobile phones and ensuring that exposures are below values taken from the ICNIRP guidelines. The values in the 1999 IEEE guidelines are used in a similar way in countries such as the USA and Canada.

1.7.1 Scientific basis

Both ICNIRP and IEEE have reviewed the broad base of the scientific evidence in developing their guidelines and arrived at similar conclusions regarding the evidence for health effects. This consensus is well expressed in the following excerpt taken from the ICNIRP 2009 restatement of its guidelines (ICNIRP, 2009b):

> It is the opinion of ICNIRP that the scientific literature published since the 1998 guidelines has provided no evidence of any adverse effects below the basic restrictions and does not necessitate an immediate revision of its guidance on limiting exposure to high frequency EMFs. The biological basis of such guidance remains the avoidance of adverse effects such as 'work stoppage' caused by mild whole body heat stress and/or tissue damage caused by excessive localized heating.

Absorption of RF fields in the body tissues leads to the deposition of energy in these tissues and this energy adds to that produced by metabolism. This energy imposes an additional thermoregulatory burden on the organism and the temperature can increase if the energy absorption rises above a certain level (see Section 1.3). Localized temperature increase can occur in response to localized absorption of energy and the core body temperature can go up in response to generalized absorption of energy throughout the body tissues. The ICNIRP guidelines (ICNIRP, 1998) conclude from the literature that:

> Established biological and health effects in the frequency range from 10 MHz to a few GHz are consistent with responses to a body temperature rise of more than 1 °C. This level of temperature increase results from exposure of individuals under moderate environmental conditions to a wbSAR of approximately 4 W/kg for about 30 minutes.

Table 1.15 Basic restrictions on SAR (W/kg), as taken from the ICNIRP and IEEE exposure guidelines

Body region	Workers/controlled			General public/uncontrolled		
	ICNIRP (1998)	IEEE (1999)	IEEE (2005)[d]	ICNIRP (1998)	IEEE (1999)	IEEE (2005)
Whole body[a]	0.4 (6)	0.4 (6)	0.4	0.08 (6)	0.08 (30)	0.08
Head and trunk [a b]	10 (6) [10]	8 (6) [1]	10 (6) [10]	2 (6) [10]	1.6 (30) [1]	2 (30) [10]
Extremities [a b c]	20 (6) [10]	20 (6) [10]	20 (6) [10]	4 (6) [10]	4 (30) [10]	4 (30) [10]

[a] In round brackets after the SAR value is the averaging time in seconds. The averaging times vary with frequency in the IEEE guidelines and the values given are for the 400 MHz to 2 GHz range typically used for mobile communication.
[b] In square brackets (where relevant) is the averaging mass in grams: the averaging mass is specified as a contiguous tissue volume by ICNIRP and as in the shape of a cube by IEEE.
[c] Extremities are taken as the hands, wrists, feet and ankles in the context of the IEEE (1999) guidelines, distal from the knees and elbows in the IEEE (2005) guidelines, and as the entire limbs in the context of the ICNIRP guidelines.
[d] The restrictions apply over the frequency range 100 kHz to 6 GHz in the case of IEEE (1999).
ICNIRP, International Commission on Non-Ionizing Radiation Protection; IEEE, Institute of Electrical and Electronics Engineers; SAR, specific absorption rate.
Compiled by the Working Group

Effects due to whole-body heating are also considered for frequencies below 10 MHz and down to 100 kHz; however, wavelength becomes progressively larger in relation to the body dimensions as frequency decreases to below 10 MHz and coupling to the fields becomes progressively weaker, with the result that less energy is absorbed. Above 10 GHz, absorption of RF fields by the body tissues becomes so strong that the RF fields are considered to be absorbed within a few millimetres of the body surface; hence the guidelines are designed to restrict surface heating.

A further class of thermal effect can be elicited with pulse-modulated RF waveforms, including certain radar signals. This effect is known as the microwave auditory effect and occurs as a result of energy absorption from successive RF pulses, causing pulsed thermal expansion of the head tissues (ICNIRP, 2009a). ICNIRP (1998) states that repeated or prolonged exposure to microwave auditory effects may be stressful and potentially harmful, and it provides additional guidance for restricting exposures to pulse-modulated fields to avoid this effect.

1.7.2 Basic restrictions

Considering the evidence relating to whole-body heating and localized heating of parts of the body, ICNIRP and IEEE have specified the basic restriction quantities shown in Table 1.15. The information presented here is a summary of the main aspects of the restrictions in the guidelines and serves to provide a simplified comparison for the purposes of this *Monograph*.

From Table 1.15 it is clear that the various sets of guidelines contain similar restriction values and have many common features. Moreover, the 2005 guidelines from IEEE have brought the ICNIRP and IEEE guidelines even closer: the SAR values are now identical and the residual differences now only pertain to averaging times, definition of the extremities, and the shape of the mass used with localized SAR restrictions.

IEEE and ICNIRP both frame their guidelines in terms of two tiers. The first tier includes a wbSAR value that is a factor of 10 lower than the 4 W/kg mentioned above, while the second tier includes restriction values that are five times lower than those in the first tier. In the case of the ICNIRP guidelines, these tiers are presented as restrictions for exposure of workers (tier 1)

Table 1.16 Basic restrictions on induced current density or induced electric field between 30 kHz and 10 MHz, as taken from the ICNIRP and IEEE exposure guidelines

Body region	Workers/controlled				General public/uncontrolled			
	ICNIRP (1998)[a] (mA/m²)	IEEE (1999)[b] (mA/m²)	IEEE (2005)[c] (mV/m)	ICNIRP (2010)[d] (mV/m)	ICNIRP (1998)[a] (mA/m²)	IEEE (1999)[b] (mA/m²)	IEEE (2005)[c] (mV/m)	ICNIRP (2010)[d] (mV/m)
Whole body	-	350	-	270	-	157	-	135
CNS	10	-	-	-	2	-	-	-
Brain	-	-	885	-	-	-	294.5	-
Heart	-	-	5647	-	-	-	5647	-
Extremities	-	-	626.9	-	-	-	626.9	-
Other tissues	-	-	626.9	-	-	-	209.3	-

[a] Peak rms current density in mA/m², averaged over 1 cm² area perpendicular to the current direction. Applies to the CNS tissues. Applicable frequency range is 1 kHz to 10 MHz.
[b] Peak rms current density in mA/m², averaged over any 1 cm² area of tissue in 1 second. Applies anywhere in the body. Applicable frequency range is 3 kHz to 100 kHz.
[c] Peak rms internal electric field in mV/m, averaged over a straight-line segment of 5 mm length, oriented in any direction. The averaging time for an rms measurement is 0.2 s. Applicable frequency range is 3.35 kHz to 5 MHz. Values are rounded to four significant digits.
[d] Internal electric field in mV/m, averaged over a contiguous tissue volume of 2 × 2 × 2 mm³. The 99th percentile value of the electric field for a specific tissue should be compared with the basic restriction. Applicable frequency range is 3 kHz to 10 MHz.
CNS, central nervous system; rms, root-mean-square value of the electric field strength
Note: All numbers denote the frequency in kHz; all limits in this frequency range increase linearly with frequency. Limits for contact currents also apply (not shown here).
Compiled by the Working Group

and the general public (tier 2). ICNIRP explains that the lower basic restrictions for exposure of the general public take into account the fact that their age and health status may differ from those of workers. The first tier in the IEEE guidelines is described as for controlled environments (subject to a RF safety programme as prescribed by IEEE) and the second tier as for uncontrolled environments, as accessible to the general public.

Electrical effects caused by stimulation of the peripheral and central nervous system are also considered below 10 MHz, although the maximum sensitivity to these effects occurs at considerably lower frequencies, in the tens of hertz to a few kilohertz region (ICNIRP, 2010). The guidelines should be referred to for further information about these effects; however, the restrictions are summarized in Table 1.16 for frequencies between 30 kHz and 10 MHz.

1.7.3 Reference levels

The guidelines also contain reference levels (called maximum permissible exposures, or MPEs, by IEEE) expressed in terms of electric- and magnetic-field strengths, or plane-wave equivalent power-density incident on the body (see Glossary). Measured or calculated values can be compared with these quantities to verify that the basic restrictions on SAR or induced current/electric fields are not exceeded.

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2. CANCER IN HUMANS

This section is a review of the large body of epidemiological evidence from studies of exposure of occupational groups and the general population to radiofrequency (RF) radiation from diverse sources, including from the use of mobile telephones. The results of these studies comprise a large amount of data, which could not be fully reproduced here. The Working Group included studies that assessed specific sources of RF radiation or job titles that were specifically linked to RF radiation. Studies that were excluded used job titles only for classification, or source surrogates only, without specifically addressing RF exposure. The Tables in this section summarize the main findings, but do not uniformly capture the results for all exposure metrics or all subgroups given in the original publications. In the text, the Working Group provides comments on those findings that are of greatest relevance to the evaluation, e.g. risk in the overall exposed group, patterns of change in risk with increasing exposure (such as a monotonic increase in risk with increasing exposure), and changes in risk with duration of exposure or latency.

2.1 Occupational exposure

The occupational environment is one domain in which humans are exposed to RF radiation. Many occupational circumstances entail regular or occasional exposure to RF radiation from fixed or mobile sources. A wide variety of workers are involved, including military and security personnel using walkie-talkie devices, radar operators, radio and television antenna maintenance and repair workers, welders performing dielectric (high-frequency) welding and sealing of plastics, workers using RF radiation for drying or testing operations, and physiotherapists employing medical diathermy equipment. Only a limited number of studies have assessed the risk of cancer in relation to either measured or inferred levels of exposure. There have been a large number of epidemiological studies of workers who were not evaluated in terms of their exposure to RF radiation, but rather with respect to their exposure to electric or magnetic fields (EMF), extremely low-frequency (ELF) fields, i.e. < 300Hz (IARC, 2002), or microwaves (MW), and an even larger number of studies in which it might be suspected that some workers were likely to have been exposed to RF radiation. The Working Group did not include these studies in the present review because it was not certain that sizable fractions of the workers in such studies were actually exposed to RF radiation, or at what levels they were exposed. This review is therefore limited to occupational studies in which the investigators made an effort to specifically document or assess exposures to RF radiation in the workers considered to be exposed.

2.1.1 Cancer of the brain

(a) Case–control studies

Thomas *et al.* (1987) conducted a death-certificate-based case–control study in selected counties of the north-eastern and southern United States of America (USA). The cases were men who had died from tumours of the brain or other parts of the central nervous system (CNS) at age ≥ 30 years between 1978 and 1981. Diagnoses were verified in hospital records. One control decedent, whose cause of death was not brain cancer, epilepsy, stroke, suicide or homicide, was selected for each case, and matched by age and year of death, and usual area of residence. The next-of-kin of the study subjects were interviewed: participation rates were 74% for cases and 63% for controls. For each job held since age 15 years, the job title and a brief description of the work, the industry, the location, the employment dates, and the hours worked per week were obtained. Two methods were used to classify men according to their occupational exposure to MW or RF radiation: one was based on a selection of broad job titles [most of which would have had mixed or predominant exposure to EMF frequencies other than RF], while in the other an industrial hygienist classified each job according to exposure to RF radiation, lead and soldering fumes. Data from 435 cases and 386 controls were analysed. Only results based on the industrial hygienist's classification are reviewed here. [While controls were individually matched to cases, there was a deficit of controls, possibly due to poorer participation, but no mention was made of adjusting for the matching variables in the analysis; thus there may have been uncorrected bias due to study design in the calculated odds ratios (ORs).] Risk of brain tumours was increased in those ever occupationally exposed to RF radiation (OR, 1.7; 95% CI, 1.1–2.7) adjusted for educational level (Table 2.1); however, the odds ratio decreased when men also exposed to soldering fumes or lead were removed from the exposed group, and dropped even further when those who might also have had exposure to organic solvents were removed from the exposed group. [This study was one of the few to directly attempt to address possible confounding of occupational exposure to RF radiation with coexposure to soldering fumes, lead and organic solvents. It was limited by the fact that it was based on death certificates (the dead controls were unlikely to accurately represent the population from which the dead cases came) and on an analysis that may not have controlled for bias due to the matched design.]

Berg *et al.* (2006) analysed data obtained from cases (glioma and meningioma) and controls using a detailed questionnaire on occupational exposure to what the authors described as RF/MW/EMF, which formed part of the data collected in the German component of the INTERPHONE study (as described in Section 2.2.2 in relation to Schüz *et al.*, 2006a). Participants were asked screening questions about use of industrial heating equipment to process food, to bond, seal, and weld materials, or to melt, dry, and cure materials. Questions were also asked about manufacturing semiconductor chips or microelectronic devices; using radar; maintaining electromagnetic devices used to treat or diagnose diseases; working with or nearby to broadcasting and telecommunications antennae and masts; using different kinds of transmitters; and using amateur ("ham") radio. When a participant screened positive for one of these activities, further questions were asked to determine whether the occupation entailed exposure to RF/MW/EMF. Each person was classified as having: no exposure (responded negatively to the screening questions, or were positive for some activities thought not to entail exposure); no probable exposure (exposure existed but probably not exposed continuously during working hours in any activity); probable exposure (probably exposed continuously during working hours in at least one activity); or high exposure

Table 2.1 Case–control studies on cancer of the brain and occupational exposure to radiofrequency radiation

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Thomas *et al.* (1987) USA, 1979–81	435	386	Death certificates of residents who had died from a cause other than brain tumour, epilepsy, stroke, suicide or homicide, matched to cases by age and year at death, and area of residence	Next-of-kin interviews regarding employment history and other risk factors for brain tumours. Exposure classified according to job title and results of previous studies, and by an industrial hygienist	Brain	*Occupational exposure to MW or RF based on assessment by the industrial hygienist*			Restricted to white men aged > 30 yr. Methods of statistical analysis were not described. Covariates: matched by age and year at death, and area of residence, but not included as covariates in the unmatched analysis
						Never exposed		1.0	
						Ever exposed		1.7 (1.1–2.7)	
						Ever exposed, excluding those with co-exposure to soldering fumes or lead		1.4 (0.7–3.1)	
						Ever exposed, excluding those with co-exposure to organic solvents	2	0.4 (NR)	

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Berg *et al.* (2006) Germany, 2000–03	381 cases of meningioma, 366 cases of glioma	1494, of whom 732 matched to glioma and 762 to meningioma cases	2449 controls frequency-matched on age, sex and centre, were derived from population registries, 63% participated. Subsequently, controls were matched to cases on a 2:1 basis	CAPI mostly in hospital for cases, and at home for controls. Interview included questions about job title and specific occupational activities followed by expert assessment of exposure to RF/MW	Glioma (C71.0–71.9; 9380–9383, 9390–9393, 9400–9401, 9410–9411, 9420–9421, 9440–9442, 9450–9451) and meningioma (C70.0; 9530–9539)	*Exposure to RF* *Glioma* Total exposure: No/not probable Probable/high exposure Probable exposure: No exposure Not probable Probable High Duration of high exposure: Not highly exposed Highly exposed for < 10 yr Highly exposed for ≥ 10 yr	 328 38 308 20 16 22 344 9 13	 1.00 1.04 (0.68–1.61) 1.00 0.84 (0.48–1.46) 0.84 (1.46–1.56) 1.22 (0.69–2.15) 1.00 1.11 (0.48–2.56) 1.39 (0.67–2.88)	Aged 30–69 yr Covariates: SES, urban or rural, exposure to ionizing radiation, smoking history, age at diagnosis

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Berg *et al.* (2006) (contd.)						*Meningioma*			
						Total exposure:			
						No/not probable	355	1.00	
						Probable/high exposure	26	1.12 (0.66–1.87)	
						Probable exposure:			
						No exposure	340	1.00	
						Not probable	15	1.11 (0.57–2.15)	
						Probable	15	1.01 (0.52–1.93)	
						High	11	1.34 (0.61–2.96)	
						Duration of high exposure:			
						Not highly exposed	370	1.00	
						Highly exposed for < 10 yr	5	1.14 (0.37–3.48)	
						Highly exposed for ≥ 10 yr	6	1.55 (0.52–4.62)	

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Karipidis *et al.* (2007) Australia, 1987–91	416	422	Population of four major centres as recorded by the electoral rolls for the Australian state of Victoria	Comprehensive job history, including self-reported RF exposure in each job, expert assessment by occupational hygienist and application of a community-based job-exposure matrix, FINJEM	Glioma (ICD-O codes 938–946)	*Total cumulative exposure to RF given by FINJEM ($W/m^2.yr$)*			Covariates: age, sex, and year of education
						Unexposed	396	1.00	
						> 0–11	4	0.57 (0.16–1.96)	
						> 11–52	8	1.80 (0.53–6.13)	
						> 52	6	0.89 (0.28–2.81)	
						P trend		0.91	
						Self-reported duration of exposure (yr) to RF			
						Unexposed	385	1.00	
						> 0–3	9	0.53 (0.23–1.21)	
						> 3–8	8	0.43 (0.18–1.00)	
						> 8	12	0.82 (0.37–1.82)	
						P trend		0.08	
						Expert assessment of duration of exposure (yr) to RF			
						Unexposed	381	1.00	
						> 0–3	10	1.20 (0.48–3.04)	
						> 3–6	12	1.65 (0.66–4.17)	
						> 6	11	1.57 (0.62–4.02)	
						P trend		0.17	

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Baldi *et al.* (2011) France, 1999–2001	221	442	Population selected from local electoral rolls and individually matched on age, sex and department of residence	Interviewer-administered face-to-face questionnaire, which included a lifetime occupational history documenting for each job held for ≥ 6 mo: job title, industry, begin and end dates, and details of tasks performed. Occupational hygienists assessed probability of exposure to RF and duration for each job.	CNS (70.0–70.9, 71.0–71.9, 72.2–72.9)	*Occupational exposure to RF* All brain tumours (n = 221): Unexposed Exposed Glioma (n = 105): Unexposed Exposed Meningioma (n = 67): Unexposed Exposed Acoustic neurinoma (n = 32): Unexposed Exposed *Amateur radio practice* All brain tumours (n = 221): No Yes	 148 7 71 7 61 0 31 1 NR NR	 1.00 1.50 (0.48–4.70) 1.00 1.44 (0.50–4.13) 1.00 - 1.00 0.40 (0.05–3.42) 1.00 1.39 (0.67–2.86)	95 males, 126 females. 70% of eligible cases participated and 69% of eligible and contactable controls. Covariates: exposure to pesticides, smoking, educational level

CAPI, computer-assisted personal interview; FINJEM, FIN(nish) job-exposure matrix; mo, month; MW, microwave; NR, not reported; RF, radiofrequency radiation; SES, socioeconomic status; W, watt; yr, year

(certainly exposed continuously during working hours and sometimes at levels > 0.08W/kg in at least one activity). Analyses included data from proxy interviews, and results were not sensitive to removal of proxy interview data. There was weak evidence that risk of glioma and of meningioma increased with increasing duration of high occupational exposure to RF/MW/EMF. For glioma, the odds ratio for < 10 years of high exposure relative to no exposure was 1.11 (95% CI, 0.48–2.56) and that for ≥ 10 years of high exposure was 1.39 (95% CI, 0.67–2.88); the analysis controlled for centre, sex, age at diagnosis, socioeconomic status, urban or rural area, exposure to ionizing radiation, and smoking history. The corresponding odds ratios for meningioma were 1.14 (95% CI, 0.37–3.48) and 1.55 (95% CI, 0.52–4.62) (Table 2.1). [The strengths of this study were its large size and evaluation of exposure at the job-activity level. Its main weaknesses included the small numbers of cases with high exposure and lack of associated consideration of other sources of exposure to RF radiation.]

Karipidis *et al.* (2007) reported on risk of glioma in relation to occupational exposure to RF radiation in a case–control study in five major population centres in the Australian state of Victoria. Cases were patients aged 20–70 years with glioma, newly diagnosed between July 1987 and December 1991, who were ascertained by screening the medical records of 14 major Melbourne (capital of Victoria) hospitals that together provided most of the neurosurgical services in the state. Completeness of ascertainment was checked against cancer-registry records of Victoria. Controls were randomly selected from the electoral rolls and frequency-matched to cases by age and sex; the electoral rolls covered about 85% of citizens at that time. Controls were excluded if they had a history of brain tumour, stroke or epilepsy. Participants completed a self-administered work-history questionnaire, which included queries about occupation, employer, industry, main tasks and duties, equipment used, start and finish dates, number of hours worked per day, number of days worked per week and whether or not they had been exposed to RF radiation, for all jobs undertaken since age 12 years that had lasted ≥ 3 months. Work histories were checked for completeness at a subsequent face-to-face interview. For 44% of cases and 2% of controls, a next-of-kin proxy completed the work history. In addition to the self-report, exposure to RF radiation was assessed from the work history by use of the Finnish National Job-Exposure Matrix (FINJEM; a community-based job-exposure matrix developed by the Finnish Institute of Occupational Health) and by review of the work histories by an expert occupational hygienist. Four categories of cumulative exposure were created for each exposure measure: unexposed, and thirds of the ranked exposure distributions for all exposed subjects. Results were adjusted for age, sex and years of schooling (a surrogate for socioeconomic status). Data on occupational exposure were obtained for 414 cases and 421 controls, i.e. 66% and 65%, respectively, of those eligible and contactable [respective numbers not contacted were not given]. With FINJEM, 18 cases and 17 controls were classified as exposed to RF radiation, 29 and 48 by self-report and 33 and 25 by expert assessment. Only in the case of classification based on expert assessment of exposure was there any consistent indication that risk of glioma increased with exposure to RF radiation: relative to those who were not exposed, odds ratios were 1.20 (95% CI, 0.48–3.04) for > 0–3 years of exposure, 1.65 (95% CI, 0.66–4.17) for > 3–6 years and 1.57 (95% CI, 0.62–4.02) for > 6 years (Table 2.1). Analyses excluding participants with proxy information showed no major differences in results. [The use of multiple measures of occupational exposure to RF radiation, including expert assessment of a comprehensive occupational history, was a strength of the study. It was limited by lack of inclusion of non-contactable subjects when estimating participation rates, by the large proportion of

cases requiring proxy respondents and by the comparatively small number of subjects who were exposed to RF radiation. FINJEM provides a probably incomplete assessment of occupational exposure to RF radiation.]

Baldi *et al.* (2011) reported on a case–control study of people aged ≥ 16 years, newly diagnosed with cancer of the primary CNS between mid-1999 and mid-2001 in the administrative region of Gironde in south-western France. Patients with neurofibromatosis, Von Hippel-Lindau disease or AIDS were excluded. Controls were selected from local electoral rolls, which automatically register all French subjects, and individually matched to cases by age, sex and department of residence. Participation rates were 70% of eligible cases and 69% of eligible and contactable controls. Occupational exposure to RF radiation was assessed by two occupational hygienists from lifetime histories of jobs that had lasted ≥ 6 months (including job title, industry, dates each job began and ended, details of tasks performed), which were collected by face-to-face interview. Information on use of amateur radio was also collected. The odds ratio for occupational exposure to RF radiation and all tumours of the brain was 1.50 (95% CI, 0.48–4.70), while for use of amateur radio it was 1.39 (95% CI, 0.67–2.86) (Table 2.1). [The Working Group noted the comparatively small size of the study and the small number of exposed subjects, which appeared to have precluded analysis at multiple exposure levels; the exposure assessment based on a comparatively limited occupational history, and an estimated participation rate for controls that was not based on all potentially eligible participants.]

(b) Cohort studies

Lilienfeld *et al.* (1978) reported on a retrospective cohort study of USA employees and their dependents who had worked or lived at the United States embassy in Moscow during 1953–1976 and, for comparison, employees and their dependents at other United States embassies in eastern Europe who had not served in Moscow over the same period. There were unusual levels of background exposure to MW in the embassy in Moscow. The maximum measured levels were 5 μW/cm^2 for 9 hours per day, 15 μW/cm^2 for 18 hours per day, and < 1 μW/cm^2 thereafter for non-overlapping time periods between 1953 and 1975 and between 1975 and 1976. Only background levels of exposure to MW were recorded in other eastern-European embassies. Relevant health information and follow-up data were obtained from the medical records of employees and their dependents (held by the Department of State) and a health-history questionnaire sent to each employee or dependent who could be located. Death certificates were sought for all decedents. The analysis was based only on subjects who could be traced (> 90%): 1719 Moscow employees and 1224 dependents known to have lived with them in the embassy, and 2460 employees at other embassies and 2072 dependents known to have lived with them. For embassy employees, 194 deaths were ascertained; of these, there was sufficient information for 181 for inclusion in the analysis, and death certificates were available for 125. There were no deaths from tumours of the brain or other parts of the CNS in Moscow employees, compared with 0.9 expected on the basis of comparable mortality rates in the USA [standardized mortality ratio, SMR, 0; 95% CI, 0–4.1). For other embassy employees, there were five deaths from tumours of the brain or other parts of the CNS, with 1.5 expected (SMR, 3.3; 95% CI, 1.1–7.7). For dependents known to have lived in the relevant embassy, > 90% were traced, 67 deaths were ascertained, 62 death certificates were available. There were no observed deaths from tumours of the brain or other parts of the CNS (0.15 expected) [SMR, 0; 95% CI, 0–24.6] for the Moscow embassy and 1 death was observed (0.19 expected) for the other embassies (Table 2.2). [This study was available only in a United States government report; it was not published in the

peer-reviewed literature. Its main weaknesses were the small sizes of the two cohorts and the small number of deaths from cancer of the CNS observed. The long and continuous exposure to high background levels of MW in the Moscow Embassy was a strength. Possible confounding factors were not addressed.]

Milham (1988a, b) followed a cohort of people who were licensed as amateur radio-operators between 1 January 1979 and 16 June 1984 (a licence was valid for 5 years) and had addresses in Washington State or California. The full names and dates of birth of male cohort members (67 829 people; there were few females) were matched with deaths in Washington State and California. Only exact matches were accepted. Person-years at risk started on the effective current registration day and ended on the day of death, or on 31 December 1984. There were 232 499 person-years at risk and 2485 deaths; 29 deaths from cancer of the brain (International Classification of Disease Revision 8 [ICD-8] code 191) were observed and 20.8 expected [the death rates used to estimate the expected numbers were not specified], SMR for deaths from cancer of the brain was 1.39 (95% CI, 0.93–2.00) (Table 2.2). Licensees were further subdivided by licence class, i.e. Novice, Technician, General, Advanced and Extra. Novices were limited in their use of transmitter power and transmission frequencies; these conditions became more liberal as licence class rose. The average age increased with rising licence class; those holding higher-level licences may have generally been amateur radio operators for longer than those holding lower-level licences. Deaths from cancer of the brain were more frequent than expected for each licence class after Novice, but with little evidence of progressive increases as licence class rose (Table 2.2). [The main strength of this study was its clear and straightforward execution. Its weaknesses included lack of information about erroneous or missed links of cohort members to deaths, lack of consideration of possible migration of cohort members from Washington State and California, limited validation of licence class as a surrogate for intensity and duration of exposure to RF radiation, and the small number of observed deaths from cancer of the brain. Possible confounding factors were not addressed.]

Armstrong *et al.* (1994) carried out a nested case–control analysis of the association of several cancers, including tumours of the brain, and exposure to pulsed electromagnetic fields (PEMFs; frequency range, 5–20 MHz) in two cohorts of electrical-utility workers in Quebec, Canada (21 749 men; follow-up, 1970–1988), and France (170 000 men; follow-up, 1978–1989), among whom 2679 cases of cancer were identified, 84 malignant tumours of the brain and 25 benign tumours of the brain. Utility-based job-exposure matrices were created with information obtained from surveys of samples of 466 (Quebec) and 829 (France) workers wearing exposure meters in 1991–1992. For malignant tumours, the odds ratios were 0.84 (95% CI, 0.47–1.50) for above-median exposure to PEMFs and 1.90 (95% CI, 0.48–7.58) for exposure at or above the 90th percentile, while for astrocytoma – the most common type of glioma – the odds ratio for exposure at or above the 90th percentile was 6.26 (95% CI, 0.30–132). For benign tumours, the odds ratio was 1.58 (95% CI, 0.52–4.78) for above-median exposure. None of the odds ratios for other subtypes of cancer of the brain were elevated (Table 2.2).

Grayson (1996) reported on risk of brain cancer related to exposure to equipment producing RF or MW (RF/MW) radiation in a case–control study conducted within a cohort of male members of the United States Air Force in 1970–89 (Table 2.2). Four matched controls were randomly selected for each case from all cohort members. Controls were not eligible if they had been diagnosed with leukaemia, cancer of the breast or melanoma "...because excess risks of these tumours have been associated with EMF exposures in other studies" [this exclusion was

not appropriate in a nested case–control study as if the excluded tumours were associated with EMF exposure, this could bias exposure in controls downwards, though probably only to a very small degree given the relative rarity of these cancers]. An expert panel assessed each job title–time couplet for probability of exposure to RF/MW radiation, which was recorded as "unexposed," "possibly exposed" and "probably exposed." Incident cases of cancer of the brain (ICD-9 code 191) were identified from hospital discharge records of serving personnel; confirmatory data (imaging or histopathology records) were not sought. Conditional logistic regression was used for the analysis; no potential confounders were included as covariates in the models. The odds ratio for cancer of the brain with ever-exposure to RF/MW was 1.39 (95% CI, 1.01–1.90). There was only weak evidence of a trend towards increasing odds ratio with increase in the value of the product of a score for probable intensity of exposure and duration of exposure. [The strengths of this study included its basis within a cohort, the careful design and the probably complete ascertainment of brain cancers occurring within the study period. It is limited by its lack of confirmation of diagnosis through access to diagnostic records, the reliance on occupational title to identify instances of potential exposure to RF/EMF radiation, and the uncertain accuracy of exposure quantification. Any bias due to these weaknesses would probably be towards the null and would weaken a dose–response relationship, if there were one.]

Szmigielski (1996) studied the incidence of cancer in the whole population of career military personnel in Poland from 1971 to 1985, averaging about 127 800 men over these 15 years. [This study appeared to be a cross-sectional study rather than a cohort study (Table 2.2).] Annual data were obtained on all career servicemen from personnel and health departments, and included numbers of servicemen, types of service posts and exposure to possible carcinogenic factors during service, while military safety groups provided information on the number of personnel exposed to RF radiation. On average, 3720 men were considered to have been exposed to RF radiation each year. It was estimated that of these, 80–85% were exposed at < 2 W/m^2 and the remainder at 2–6 W/m^2, but individual exposure levels could not be assigned. Exposure was largely to pulse-modulated RF radiation at 150–3500 MHz. Annual data on all men newly diagnosed with cancer were collected from records of military hospitals and the military medical board; in addition to type of cancer, they included duration and type of service and exposure to possible carcinogenic factors during service, including whether or not they were exposed to RF radiation. [It was unclear from the text whether information in individual health records may have been used, in addition to information applicable to all servicemen, in allocating a man diagnosed with cancer to the group exposed to RF radiation.]

[It appeared to the Working Group that these data were insufficient to permit calculation of annual age-specific rates of all cancers (in age groups of 10 years) and individual types of cancer in men exposed to RF radiation and men not exposed and thus to calculate ratios of incidence in the exposed group to that in the unexposed group for each year and for the whole period. The methods were described in limited detail and it was not stated how the rates or rate ratios were summarized across age groups and years and, in particular, whether cancer-incidence rate ratios based on all exposed and all unexposed men were age-standardized. The observed numbers of cases of all cancers or individual types of cancer were not presented, but could be approximated from average annual rates of incidence, from which it appeared that two to three cases of cancer of the nervous system and brain (ICD codes not specified) were diagnosed in men exposed to RF radiation over the 15 years, and about 54 cases in men not exposed.]

Table 2.2 Cohort studies of cancer of the brain and occupational exposure to radiofrequency radiation

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Lilienfeld *et al.* (1978) United States embassies in eastern Europe	7475	1953–76	Worked or lived in the United States embassy in Moscow during study period. The maximum measured levels were 5 μW/cm^2 for 9 h/d, 15 μW/cm^2 for 18 h/d, and < 1 μW/cm^2 thereafter for non-overlapping periods between 1953 and 1975 and between 1975 and 1976	Brain and CNS (ICD-7 code 193)	*Role and location in eastern Europe*		SMR	Sex, age	SMRs are relative to the corresponding mortality rates in the USA. Contract report is available through the National Technical Information Service of the USA.
					Employed in the United States embassy in Moscow	0	0 [0–4.1]*		
					Dependent of a Moscow United States embassy employee	0	0 [0–24.6]*		
					Employed in a different United States embassy in eastern Europe	5	3.3 [1.1–7.7]*		
					Dependent of an employee at a different United States embassy in eastern Europe	1	5.3 [0.13–29]*		
Milham (1988a, b) USA	67 829	1979–84	Licensing as an amateur radio operator	Brain (191)	*Amateur radio operator licence class*		SMR		
					Novice	1	0.34		
					Technician	4	1.12		
					General	11	1.75		
					Advanced	11	1.74		
					Extra	2	1.14		
					All	29	1.39 (0.93–2.00)		

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Armstrong *et al.* (1994) Canada and France	191 749	1970–89	Exposure assessed through a job-exposure matrix based on about 1000 person-weeks of measurements from exposure meters worn by workers to derive estimates of short-duration PEMFs, or high-frequency transient fields.	Brain (191)	*PEMFs*		OR	SES	Nested case–control analysis. Controls for each case were selected at random from the cases risk set and matched by utility and year of birth. Exposure was counted only up to the date of diagnosis of the case.
					Malignant cancer of the brain:				
					< Median	49	1.00		
					> Median	35	0.84 (0.47–1.50)		
					≥ 90th percentile	9	1.90 (0.48–7.58)		
					Astrocytoma:				
					< Median	22	1.00		
					> Median	12	0.89 (0.29–2.67)		
					≥ 90th percentile	3	6.26 (0.30–132)		
					Glioblastoma:				
					< Median	16	1.00		
					> Median	13	0.49 (0.19–1.28)		
					≥ 90th percentile	5	0.57 (0.08–3.91)		
					Other cancers:				
					< Median	7	1.00		
					> Median	6	2.67 (0.43–16.71)		
					≥ 90th percentile	1	-		
					Benign tumours of the brain:				
					< Median	9	1.00		
					> Median	16	1.58 (0.52–4.78)		
					≥ 90th percentile	1	-		

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Grayson (1996) USA	230 cases, 920 controls	1970–89	Job title-time-exposure matrix. Census of control histories was carried out at time of matched case's diagnosis. Exposure score was the sum of the products of duration of deployment in each job and the assessed probability of RF exposure in that job at that time.	Brain (191)	*RF/MW*		OR	Controls exactly matched to case on year of birth, race and presence in the cohort at the time when the case was diagnosed. Matching retained in analysis. Age, race, rank (senior or other) included as covariates.	United States Air Force personnel Nested case–control analysis within cohort study. All male members of United States Air Force. Rank associated with risk; senior officers at increased risk.
					Never exposed	94	1.00		
					Exposed	136	1.39 (1.01–1.90)		
					RF/MW exposure score				
					None	136	1.00		
					2–48	15	1.26 (0.71–2.24)		
					49–127	29	1.50 (0.90–2.52)		
					128–235	25	1.26 (0.71–2.22)		
					236–610	25	1.51 (0.90–2.51)		
Szmigielski (1996) Poland	Average of 127 800 men, yearly during 15 yr	1971–85	Military safety (health and hygiene) groups classified military service posts as having exposure, or not, to RF	Nervous system, including brain	*Occupational exposure to RF*			None specified	Cross-sectional study. Incidence rate ratio for all cancers, 2.07 (95% CI, 1.12–3.58) suggests possible upward bias in rate ratios.
					Not exposed	[54]*	1.00		
					Exposed	[2–3]*	1.91 (1.08–3.47)		
					P value		< 0.05		
Tynes *et al.* (1996) Norway	2619 women	1961–91	Radio and telegraph operators with potential exposure to RF and ELF	Brain (ICD-7 code 193)	Radio and telegraph operators with potential exposure to RF and ELF	5	SIR, 1.0 (0.3–2.3)	Age, time since certification, calendar year, age at first childbirth	Women certified as radio and telegraph operators 1920–80

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Lagorio *et al.* (1997) Italy	481 women	1962–92	Occupational history from plant records. RF generated by dielectric heat sealers. Exposure of 10 W/m^2 equivalent power-density frequently exceeded.	Brain (191)	*Job title*			Sex, age, calendar period-specific regional person-year at risk	Mortality analysis restricted to women
					RF-sealer operators	1	10 [0.25–56]*		
					Other workers	0	0 [0–46]*		
					All female workers	1	5 [0.13–28]*		
Morgan *et al.* (2000) USA	195 775 Motorola employees	1976–96	Job-exposure matrix	Brain/CNS	*Cumulative exposure to RF*		*Rate ratio*	Age, sex, and race for external comparisons; and age, sex, and period of hire for internal comparisons	All employees of Motorola; exposure from cellular phones not assessed. Definition of exposure categories unclear.
					None	34	1.00		
					< Median	7	0.97 (0.37–2.16)		
					≥ Median	10	0.91 (0.41–1.86)		
					Usual exposure to RF				
					None	38	1.00		
					Low	7	0.92 (0.43–1.77)		
					Moderate	3	1.18 (0.36–2.92)		
					High	3	1.07 (0.32–2.66)		
					Peak exposure to RF				
					None	34	1.00		
					Low	10	0.98 (0.50–1.80)		
					Moderate	3	0.70 (0.21–1.77)		
					High	4	1.04 (0.36–2.40)		
					Duration of exposure				
					None	44	1.00		
					≤ 5 yr	3	0.74 (0.22–1.84)		
					> 5 yr	4	0.99 (0.35–2.26)		
					Cumulative exposure to RF				
					Males-low	23	1.00		
					Males-high	8	1.11 (0.38–2.78)		
					Females-low	18	1.00		
					Females-high	2	0.58 (0.03–3.30)		

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Groves *et al.* (2002) USA	40 581 men (271 women excluded)	1950–97	United States Navy personnel with potential for RF exposure; job classified as entailing low or high exposure	Brain (ICD-9 codes 191.0–191.9)	*Job-associated exposure to RF*		*SMR*	Age at cohort entry, attained age	White United States Navy (male) veterans of Korean War (1950–54)
					Low	51	1.01 (0.77–1.33)		
					High	37	0.71 (0.51–0.98)		
					Total cohort	88	0.86 (0.70–1.06)		
					Within-cohort comparison:				
					Low exposure	51	1.00		
					High exposure	37	0.65 (0.43–1.01)		
Degrave *et al.* (2009) Belgium	Military personnel (4417 men) in batallions equipped with radar, and 2932 controls	1968–2003	Exposure levels on the site where the battalion lived and worked were characterized, individual exposure assessment could not be conducted.	Cancer of eye, brain and nervous system (190–192)	Control cohort	2	1.00		Cause of death found for 71% of the men in the radar group and 70% in the control group.
					Radar-exposed	8	2.71 (0.42–17.49)		

* values calculated/deduced by the Working Group

d, day or days; ELF, extremely low-frequency electric and magnetic field; h, hour or hours; mo, month; MW, microwaves; OR, odds ratio; PEMFs, pulsed electromagnetic fields; RF, radiofrequency radiation; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; W, watt; yr, year

The incidence rate ratio (IRR) for cancer of the nervous system and brain over the 15 years in those exposed to RF radiation was estimated to be 1.91 (95% CI, 1.08–3.47). The corresponding incidence rate ratio for all cancers was 2.07 (95% CI, 1.12–3.58). [The similarity of these two incidence rate ratios suggested the possibility of consistent upward bias in their estimation. It also appeared that the 95% confidence intervals had not been correctly calculated given their similar width and the large difference in the observed numbers on which they were based: 2–3 cancers of the nervous system and brain and about 32 cancers of all types.] Age-specific incidence rate ratios for all cancers ranged from 2.33 at age 20–29 years to 1.47 at age 50–59 years. [This was somewhat against the hypothesis that failure to standardize by age had increased the incidence rate ratios with exposure to RF radiation. The interpretation of this study was hampered by its cross-sectional design, in which risk of cancer was related only to current exposure to RF radiation; uncertainty about the accuracy of the classification of exposure; lack of a quantitative measure of exposure; lack of information on completeness of ascertainment of cancer incidence; lack of clarity concerning the analytical methods, including whether incidence rate ratios were age-standardized; and probable errors in the statistical analysis. Possible confounding factors were not addressed. The possibility that medical records accessed for men with cancer may have provided information that led them to being classified as exposed to RF radiation may explain the apparently high risks of cancer in men exposed to RF radiation in this study.]

Tynes *et al.* (1996) examined incidence of cancer in a cohort of 2619 Norwegian women who were certified as radio and telegraph operators between 1920 and 1980 (Table 2.2); 98% had worked on merchant navy ships. They were followed from 1961 to 1991 via the Norwegian cancer registry; 41 were lost to follow-up. Electric and magnetic fields were measured in the radio rooms of three older Norwegian ships. They were below detection levels at radio-frequencies at the operators' desks and were considered to be comparable to those found at normal Norwegian workplaces. The age- and calendar period-adjusted standardized incidence ratio (SIR) for cancers of the brain and nervous system (ICD-7 code 193) was 1.0 (95% CI, 0.3–2.3; based on five cases) with reference to the national Norwegian female population. [The strengths of this study were its homogeneous cohort and near-complete follow-up; its principal weaknesses were the small number of cases of brain cancer and the probably low exposure of the cohort to RF radiation. Possible confounding factors were not addressed.]

Lagorio *et al.* (1997) reported on mortality from all causes and from specific cancers in a group of 201 men and 481 women employed in a plastic-ware manufacturing facility in Grossetto, Italy, from 1962 to 1992 and followed until death, or until the end of 1992 (Table 2.2) Those lost to follow-up were considered to be alive at the end of 1992. Vital status and cause of death were ascertained from the registry office of the municipality of residence and death. Workers were classified into three groups: RF-sealer operators, other labourers and white-collar workers. RF-sealer operators received the greatest exposure to RF radiation. They were also exposed to vinyl chloride monomer due to its volatilization from polyvinyl chloride (PVC) sheets during sealing. At the end of follow-up, 661 subjects were alive, 16 had died and 5 were lost to follow-up [details of tracing methods were not given]. The mortality analysis was restricted to women, who were mostly employed in the manufacturing department (6772 person-years in RF-sealer operators). There was one death ascribed to a tumour of the brain and 0.2 expected based on mortality rates in the regional population; this single death occurred in an RF-sealer operator (expected, 0.1). [The principal weakness of this study was its

small size. Possible confounding from exposure to vinyl chloride was not addressed.]

Morgan *et al.* (2000) studied a cohort of all employees of Motorola USA with at least 6 months of cumulative employment, who were employed for at least 1 day between 1976 and 1996, and followed to 31 December 1996. Deaths were ascertained through reference to the Social Security Administration Master Mortality File and the National Death Index. Death certificates were obtained from the state vital statistics offices and company benefits records, and causes of death were coded according to ICD-9. There were 195 775 workers, 2.7 million person-years of follow-up and 6296 deaths, 53 of which were attributed to cancer of the CNS [ICD-9 codes not stated]. No losses to follow-up were reported [it is probable that the 116 700 workers who had retired or whose employment had been terminated were assumed to be alive if no death record was found for them]. Exposure to RF radiation was assessed on the basis of a company-wide job-exposure matrix, developed through expert consultation, that categorized each of 9724 job titles into one of four exposure groups: background, low, moderate, and high, corresponding roughly to < 0.6 W, 0.6– < 2.0 W, 2.0– < 5.0 W, 5.0– < 50 W and ≥ 50 W. About 45 500 employees were thought to have had usual exposures of ≥ 0.6 W, 8900 employees had a high usual exposure (≥ 50 W) and 9000 employees had unknown usual exposure. Relative to mortality in the combined populations of Arizona, Florida, Illinois, and Texas, where most Motorola facilities were located, the SMR for tumours of the CNS was 0.60 (95% CI, 0.45–0.78). Internal comparisons between categories of estimated cumulative, usual and peak exposure to RF radiation; duration of exposure; (cumulative exposure lagged 5, 10 and 20 years) and cumulative exposure in males and females separately, showed no consistent evidence of an increase in risk of tumours of the CNS with increasing estimated exposure to RF radiation (Table 2.2). [The main strength of this study was the clear and straightforward execution and comprehensive analyses. Its weaknesses included lack of measured exposure to RF radiation on which to base the exposure classification; inadequate description of the exposure-validation study; lack of detail on how the links between cohort members and death records were established, and therefore uncertainty about completeness and accuracy of death ascertainment; the comparatively small number of observed deaths from tumours of the CNS; and possible conservative bias due to exclusion of mobile-phone use from the estimate of exposure to RF radiation. Possible confounding factors were not addressed.]

Groves *et al.* (2002) reported on an extended follow-up to death or to the end of 1997 for 40 890 United States Navy personnel originally studied by Robinette *et al.* (1980). These men were graduates of Class-A Navy technical training schools who had served on ships in the Korean War during 1950–54, and who had potentially been exposed to high-intensity radar. They were divided into two occupational groups considered by a consensus of Navy personnel involved in training and operations to have had high exposure to RF radiation (electronics, fire-control and aviation-electronics technicians: 20 109 men) or low exposure (radiomen, radar men and aviation electricians' mates: 20 781 men). Potential exposure in each job category was evaluated from the records for 435 men who had died and those of a randomly selected 5% of living men as "the sum of all power ratings of all fire control radars aboard the ship or search radars aboard the aircraft to which the technician was assigned multiplied by the number of months of assignment." Ascertainment of death required use of Department of Veterans' Affairs and Social Security Administration records and the National Death Index. [Its completeness was uncertain.] It was necessary to impute moderate proportions of dates of entry into the cohort (1950–54) and dates of birth, because of missing

data. The analysis was limited to 40 581 men and SMRs were calculated with reference to all white men in the USA, standardized for age at entry to the cohort and attained age. Altogether, there were 51 deaths from cancer of the brain (ICD-9 codes 191.0–191.9); there was no evidence of any increase in risk of cancer of the brain associated with high exposure to RF radiation (Table 2.2). The SMRs for cancer of the brain were 0.86 (95% CI, 0.70–1.06) for the whole cohort, 1.01 (95% CI, 0.77–1.33) for the group with low exposure to RF radiation (usual exposures well below 1 mW/cm^2) and 0.71 (95% CI, 0.51–0.98) for the group with high exposure to RF radiation (potential for exposures up to 100 kW/cm^2, but usually less than 1 mW/cm^2). Within the cohort, the relative risk (RR) of death from cancer of the brain in the group with high exposure to RF radiation relative to the group with low exposure was 0.65 (95% CI, 0.43–1.01). [This appeared to have been an initially somewhat poorly documented cohort, for which follow-up was difficult and some missing data, including birth date, had to be imputed. While expert assessment permitted division of the cohort into groups with low and high exposure to RF radiation, no specific measurements of exposure were reported. Assessment of exposure appeared to have been limited to 1950–54. Possible confounding factors, such as occupational exposure to other agents, were not addressed.]

In a cohort of 4417 Belgian male professional military personnel who served in battalions equipped with radar for anti-aircraft defence, cause-specific mortality was compared with that of 2932 Belgian military personnel who served in battalions not equipped with radar (Degrave *et al.*, 2009). Administrative archives of the battalions were used to reconstruct a list of personnel serving in each battalion. Lists were matched to those of the Department of Human Resources of the Belgian Army to find the subjects' birthdays, which allowed retrieval of their Belgian national identity number. With this number, mortality follow-up could be conducted. For military personnel who died before 1979, the registry only recorded month and year of birth, and thus for 35 dead military exact birth-dates were not available, matching was equivocal and the cause of death was not used. The registry was complete until 1997 and from 1998 to 2004, only for the northern, Dutch-speaking part of Belgium. In parallel, for all professional military personnel who died up to 31 December 2004, first-degree family members were sought and a questionnaire sent to enquire about likely cause of death. For the period of follow-up of this study, the Belgian cancer registry was incomplete, but the information on cases of cancer reported to the registry was reliable. Thus the cancer registry was used only for confirmation, but not for identification of cancer cases. The risk ratio for deaths from cancers of the eye, brain and nervous system in the cohort serving in battalions equipped with radar compared with the unexposed cohort was 2.71 (95% CI, 0.42–17.49) (Table 2.2). [The Working Group noted the difficulties in following-up the study population that may have affected the study results, as well the difficulty of attributing any possible increase in risk ratio to exposure to RF radiation, given possible confounding due to ionizing radiation also emitted by devices producing MW radiation.]

2.1.2 Leukaemia and lymphoma

(a) Case–control studies

No data were available to the Working Group.

(b) Cohort studies

Lilienfeld *et al.* (1978) reported on a retrospective cohort study of USA employees, and their dependents, who had worked or lived at the United States embassy in Moscow during 1953–76 (see Section 2.1.1 for details). The total risk ratio for leukaemia in the embassy employees was 2.5 (95% CI, 0.3–9.0).

Milham (1988a, b) followed a cohort of people who were licensed as amateur radio operators between 1 January 1979 and 16 June 1984 (see Section 2.1.1 for details). There was a borderline excess risk of death from lymphatic and haematopoietic neoplasms, from acute myeloid leukaemia, and from multiple myeloma and lymphoma (Table 2.3). There was no evidence for an increase in SMR for these neoplasms with higher license class (see Section 2.1.1. for discussion of the strengths and weaknesses of this study).

Armstrong *et al.* (1994) conducted a nested case–control study of cancers at different sites within cohorts of electrical workers in Quebec, Canada, and in France (see Section 2.1.1 for details). There were no excess risks for all haematological cancers, non-Hodgkin lymphoma (NHL) or for all leukaemias, or for any of the subtypes of leukaemia, associated with exposure to PEMF (Table 2.3). [The strengths and weaknesses of this study are described in Section 2.1.1.]

The study by Szmigielski (1996) is described in detail in Section 2.1.1. A significantly increased incidence rate ratio for cancers of the haematological system and lymphatic organs was reported (Table 2.3). [The results were difficult to interpret, as there were many methodological flaws in the design and analysis of the study. Main issues were that exact data on the age of the subjects in the cohort were missing and that collection of exposure data was potentially differential.]

Tynes *et al.* (1996) followed a cohort of 2619 Norwegian women who were certified as radio and telegraph operators between 1920 and 1980. There was no elevation in risk of lymphoma or leukaemia for those potentially exposed to RF radiation (Table 2.3). [The strengths of this study are discussed in Section 2.1.1; its principal weaknesses were the small number of cancer cases and the probably low exposure of the cohort to RF radiation. Possible confounding factors were not addressed.]

Lagorio *et al.* (1997) reported on mortality from all causes and from specific cancers in a group of plastic sealers in Italy (see Section 2.1.1 for details). There was one death (0.2 expected) ascribed to leukaemia in an RF-sealer operator (Table 2.3). [The principal weakness of this study was its small size. Possible confounding factors were not addressed.]

Morgan *et al.* (2000) reported on a 20-year follow-up of 195 775 employees of Motorola USA (described in Section 2.1.1) and considered death from lymphatic and haematopoietic malignancies (Table 2.3). Of these, there were 87 deaths from leukaemia, 19 from Hodgkin disease and 91 from NHL. Reduced odds ratios for lymphatic and haematopoietic malignancies and subtypes were seen among workers categorized as exposed (compared with non-exposed workers) in most categories of estimated exposure, duration of exposure and cumulative exposure lagged 5, 10 and 20 years. [The Working Group noted the small number of deaths from lymphoma and leukaemia in the exposed cohort, which, together with the other limitations mentioned in Section 2.1.1, complicated the interpretation of these findings.]

Richter *et al.* (2000) collected data on six patients claiming compensation for their cancer who visited the Unit of Occupational and Environmental Medicine at the Hebrew University-Hatlawah Medical School, Jerusalem in 1992–99. They were judged to have received high RF/MW radiation based on self-reports, information from manuals containing specifications of the equipment they had used and repaired, and results of sporadic measurements from their work and medical records. A study was then conducted of 25 co-workers of one of the patients and of other personnel with self-reported exposure to RF radiation. An increased risk of haematolymphatic malignancies was found (5 cases observed compared with 0.02 cases expected among Jewish men aged 20–54 years). [The Working Group noted that the results of

this study were very difficult to interpret, due to unclear definition of the study population, follow-up and exposure assessment.]

Groves *et al.* (2002) reported on mortality in a cohort of 40 890 male United States Navy personnel who had served on ships during the Korean War in 1950–54 in an extended follow-up to 1997 (described in more detail in Section 2.1.1). The cohort was divided into two subgroups on the basis of job title, with potential exposure to RF radiation based on expert assessment: 20 109 workers comprising a subcohort with high exposure to RF radiation (potential for exposures up to 100 kW/cm^2, but usually < 1 mW/cm^2) and a subcohort of 20 781 workers with low exposure (usually well below 1 mW/cm^2). A total of 182 deaths from lymphoma or multiple myeloma (91 each in the high- and low-exposure subcohorts) and 113 deaths from leukaemia (44 and 69 in the high- and low-exposure subcohorts, respectively) were identified in 1950–97. In both subcohorts, SMRs were not elevated for lymphoma and multiple myeloma, all leukaemias, lymphocytic leukaemia or non-lymphocytic leukaemia (Table 2.3). An internal comparison of high relative to low exposure to RF radiation elicited RRs of 0.91 (95% CI, 0.68–1.22) for lymphoma and multiple myeloma, 1.48 (95% CI, 1.01–2.17) for all leukaemias, 1.82 (95% CI, 1.05–3.14) for non-lymphocytic leukaemia and 1.87 (95% CI, 0.98–3.58) for acute non-lymphocytic leukaemia. An increased risk of all leukaemias was observed primarily in aviation-electronics technicians (RR, 2.60; 95% CI, 1.53–4.43, based on 23 deaths) and was highest for acute myeloid leukaemia (RR, 3.85; 95% CI, 1.50–9.84, based on 9 deaths). RRs for other job categories with high exposure were close to 1. This was interpreted as indicating a possible association, since aviation-electronics technicians who dealt primarily with mobile radar units may have had more potential to enter the beam path of an operating radar than members of other groups who worked with ship-mounted radars. [The limitations of this study are discussed in Section 2.1.1, including limitations in the documentation of the cohort definition and difficulties in follow-up. Classification of exposure to RF radiation in the different groups was based on expert assessment. No measurement of RF radiation was provided.]

Degrave *et al.* (2009) compared a cohort of 4417 Belgian male professional military personnel who served in battalions equipped with radars for anti-aircraft defence with 2932 Belgian male professional military personnel who served at the same time in the same place in battalions not equipped with radars. Attempts were made to characterize exposure levels on the site where the battalion lived and worked, but individual exposure assessment could not be conducted. Administrative archives of the battalions were used to reconstruct a list of personnel serving in each battalion. These archives only provided first name, family names, and a unique identification number. Lists were matched to those of the Department of Human Resources of the Belgian Army to find the subjects' birthdays, which allowed retrieval of their Belgian national identity number. With this number, mortality follow-up could be conducted. The first source of information on cause of death was the official Belgian death registry, which collects anonymous data. Linkage was conducted using date of birth and date of death as matching variables (cause of death could be found for 71% of persons in the radar group and 70% in the control group). For military personnel who died before 1979, the registry only recorded month and year of birth, and exact birth-dates were not available for 35 of the dead, while matching was equivocal and the cause of death was not used. The registry was complete until 1997 and from 1998 to 2004, only for the Northern, Dutch-speaking part of Belgium. In parallel, for all professional military personnel who died up to 31 December 2004, first-degree family members were sent a questionnaire to enquire about the likely cause of death. For the period of follow-up of this study,

Table 2.3 Cohort studies of leukaemia and occupational exposure to radiofrequency radiation

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Lilienfeld *et al.* (1978)	7475	1953–76	Worked or lived in the United States embassy in Moscow during study period. The maximum measured levels were 5 μW/cm^2 for 9 h/d, 15 μW/cm^2 for 18 h/d, and < 1 μW/cm^2 thereafter for non-overlapping periods 1953–1975 and 1975–1976	Leukaemia	Embassy employees		2.5 (0.3–9.0)	Sex, age	SMRs are relative to the corresponding mortality rates in the USA. Contract report is available through the National Technical Information Service of the USA.
Milham (1988a, b) USA	67 829	1979–1984	Licensing as an amateur radio operator	Lymphatic and haematopoietic cancers			*SMR*		The death rates used to estimate the expected numbers were not specified
					All leukaemia	89	1.23 (0.99–1.52)		
					AML	36	1.24 (0.87–1.72)		
					Multiple myeloma and lymphoma	15	1.76 (1.03–2.85)		
					All lymphatic and haematopoietic cancers	43	1.62 (1.17–2.18)		
					By licence class:				
					Novice	9	1.01 [0.46–1.92]*		
					Technician	18	1.63 [0.97–2.58]*		
					General	26	1.19 [0.78–1.74]*		
					Advanced	27	1.15 [0.76–1.67]*		
					Extra	9	1.34 [0.61–2.54]*		

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Armstrong *et al.* (1994) Canada and France	191 749	1970–89	Exposures assessed through a job-exposure matrix based on about 1000 person-weeks of measurements from exposure meters worn by workers to derive estimates of short-duration PEMFs, or high-frequency transient fields.	Haematological	*PEMFs*		OR	SES	Nested case–control analysis Controls for each case were selected at random from the cases risk set, and matched to the case by utility and year of birth. Exposure was counted only up to the date of diagnosis of the case.
					All haematological cancers:				
					< Median	167	1.00		
					> Median	135	0.90 (0.65–1.25)		
					≥ 90th percentile	28	0.96 (0.48–1.90)		
					NHL:				
					< Median	54	1.00		
					> Median	56	1.41 (0.83–2.38)		
					≥ 90th percentile	13	1.80 (0.62–5.25)		
					All leukaemias:				
					< Median	57	1.00		
					> Median	38	0.69 (0.40–1.17)		
					≥ 90th percentile	9	0.80 (0.19–3.36)		
Szmigielski (1996) Poland	Average of 127 800 men, yearly during 15 yr	1971–85	Military safety (health and hygiene) groups classified military service posts as having exposure, or not, to RF	Cancer of the haematopoietic system and lymphatic organs	*Occupational exposure to RF*		Incidence rate ratios	None specified	Cross-sectional study
					Not exposed	[131]*	1.00		
					Exposed	[24]*	6.31 (3.12–14.32)		
Tynes *et al.* (1996) Norway	2619 women	1961–91	Radio and telegraph operators with potential exposure to RF and ELF fields	Lymphoma (ICD-7 code 201) Leukaemia (ICD-7 code 204)	*Potential exposure*		*SIR*	Age, time since certification, calendar year, age at first childbirth	Women certified as radio and telegraph operators, 1920–80
					Lymphoma	5	1.3 (0.4–2.9)		
					Leukaemia	2	1.1 (0.1–4.1)		

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Lagorio *et al.* (1997) Italy	481 women	1962–92	Occupational history from plant records. RF generated by dielectric heat sealers. Exposure of 10 W/m^2 equivalent power-density frequently exceeded.	Leukaemia (204–208)	*Job title*		*SMR*	Sex, age, calendar period-specific regional person-year at risk	Mortality analysis; restricted to women
					RF-sealer operators	1	[5.0 (1.27–27.85)]*		
					Other workers	1	[11.1]*		
					All female workers	2	8.0 (1.0–28.8)		
Richter *et al.* (2000) Israel	Co-workers (n = 25) of one of the six patients claiming compensation for their cancer, and other personnel with self-reported exposure to RF	1992–99	Self-reports, information from manuals containing specifications of the equipment they had used and repaired, and results of sporadic measurements from their work and from medical records.	Haemato-lymphatic malignancies	Jewish men aged 20–54 yr	5	*SIR* [250 (81.17–583.42)]*	None	[The Working Group noted that the results of this study were very difficult to interpret, due to unclear definition of the study population, follow-up, and exposure assessment.]

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Morgan *et al.* (2000) USA	195 775	1976–96	Job-exposure matrix, developed through expert consultation that categorized each of 9724 job titles into different RF exposure groups: background, low, moderate, and high, corresponding roughly to < 0.6 W, 0.6 to < 2.0 W, 2.0 to < 5.0 W, 5.0 to < 50 W and ≥ 50 W, respectively	All lymphatic/ haematopoietic cancers (n = 203)	*Cumulative exposure to RF*		Rate ratio	Age, sex, and race for external comparisons; and age, sex, and period of hire for internal comparisons	All employees of Motorola; exposure from cellular telephones not assessed. Definition of exposure categories unclear
					None	148	1.00		
					< Median	21	0.74 (0.39–1.28)		
					> Median	34	0.67 (0.40–1.05)		
					Usual exposure to RF				
					None	152	1.00		
					Low	28	0.94 (0.57–1.47)		
					Moderate	10	0.90 (0.39–1.78)		
					High	8	0.70 (0.27–1.47)		
					Peak exposure to RF				
					None	145	1.00		
					Low	34	0.79 (0.49–1.23)		
					Moderate	11	0.58 (0.25–1.13)		
					High	10	0.60 (0.49–1.23)		
					Duration of exposure				
					None	182	1.00		
					≤ 5 yr	5	0.29 (0.12–0.57)		
					> 5 yr	16	0.89 (0.55–1.35)		
					Cumulative exposure to RF				
					Males-low	109	1.00		
					Males-high	19	0.53 (0.39–0.72)		
					Females-low	60	1.00		
					Females-high	15	1.12 (0.22–3.90)		

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Groves *et al.* (2002) USA	40 581 men (271 women excluded)	1950–97	United States Navy personnel with potential exposure to RF; job classified as having low or high exposure by a consensus of Navy personnel involved in training and operation	All haematopoietic cancers (200–208)	*Job-associated exposure to RF*		*SMR*	Age at cohort entry and attained age	White (male) United States Navy veterans of Korean War (1950–54) Reference: all white men, USA Group of aviation-electronics technicians: RR 2.60 (1.53–4.43) for all leukaemias; RR 3.85 (1.50–9.84) for acute myeloid leukaemia
					Lymphoma and multiple myeloma:				
					Low	91	0.94 (0.77–1.16)		
					High	91	0.89 (0.72–1.09)		
					All leukaemias:				
					Low	44	0.77 (0.58–1.04)		
					High	69	1.14 (0.90–1.44)		
					Lymphocytic leukaemia:				
					Low	17	1.31 (0.81–2.11)		
					High	16	1.12 (0.69–1.83)		
					Non-lymphocytic leukaemia:				
					Low	20	0.67 (0.43–1.04)		
					High	39	1.24 (0.90–1.69)		

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Degrave *et al.* (2009) Belgium	Military personnel (4417 men) in batallions equipped with radar, and 2932 controls	1968–2003	Exposure levels on the site where the battalion lived and worked were characterized; individual exposure assessment could not be conducted.	Cancer of lymphatic and haematopoietic tissue (200–208)	Control cohort Radar exposed	1 11	1.00 7.22 (1.09–48.9)		Cause of death found for 71% of the men in the radar group and 70% in the control group

* values calculated/deduced by the Working Group

AML, acute myeloid leukaemia; ELF, extremely low frequency electric and magnetic field; MW, microwaves; NHL, non-Hodgkin lymphoma; OR, odds ratio; PEMFs, pulsed electromagnetic fields; RF, radiofrequency radiation; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; W, watt; yr, year

the Belgian cancer registry was extremely incomplete, but the information on cases of cancer reported to the registry was reliable. Thus, the cancer registry was used only for confirmation but not for identification of cancer cases. The relative risks were estimated, adjusting for age in 10-year categories with a Poisson regression model. There were 11 deaths from lymphatic and haematopoietic neoplasms in the radar battalion compared with 1 in the unexposed cohort (RR, 7.22; 95% CI, 1.09–48.9) (Table 2.3). [The Working Group noted the difficulties in following-up the study population, which may have affected the study results, as well the difficulty in attributing any possible increase in relative risk to exposure to RF radiation, given possible confounding due to ionizing radiation also emitted by devices producing MW radiation.]

2.1.3 Uveal (ocular) melanoma

Stang *et al.* (2001) conducted population-based and hospital-based case–control studies of uveal melanoma and occupational exposures to different sources of electromagnetic radiation, including RF radiation. For the population-based study, 37 cases were identified by a reference pathologist (response rate, 84%) and 327 controls were sampled and matched from the same region of residence, age and sex (response rate, 48%). For the hospital-based study, the 81 cases were patients treated at the University of Essen (response rate, 88%) and controls (n = 148) were patients with benign intra-ocular tumours (response rate, 79%). The results of these studies were pooled.The 118 female and male cases and 475 controls were interviewed by a trained interviewer with a structured questionnaire involving medical history, lifestyle, occupation and occupational exposure to RF radiation. Participants were specifically asked about exposure to radar and to other RF-emitting devices ("Did you use radio sets, mobile phones or similar devices at your workplace for at least several hours per day?") and more detail was obtained from those who reported exposure. Additional information provided by exposed participants was used by two of the authors, working independently and unaware of case or control status, to classify them as: exposed only to radio receivers that do not transmit RF radiation and therefore unexposed; exposed to RF radiation from walkie-talkies and radio sets; possibly exposed to RF radiation from mobile phones; and probably or certainly exposed to RF radiation from mobile phones. Few participants reported occupational exposure to radar. The odds ratio for uveal melanoma was 0.4 (95% CI, 0.0–2.6). For exposure to radio sets, the odds ratio was 3.3 (95% CI, 1.2–9.2) (Table 2.4). Adjustment for socioeconomic status or iris/hair colour did not alter these results. The results for reported occupational use of mobile phones are considered in Section 2.3. [This study was weakened by its poor assessment of occupational exposure to RF radiation, particularly the retrospective classification of exposure to other RF-emitting devices, although neither should be a source of positive bias. Confounding of occupational exposure to RF radiation with exposure to ultraviolet light from the sun or other sources was not considered and may have been important if, for example, much of the use of radio sets had entailed use of walkie-talkie radios for communication outdoors.]

2.1.4 Cancer of the testis

(a) Case–control studies

Interpretable results were available from only two case–control studies (Table 2.5). Both were limited by reliance on self-report for exposure classification.

Hayes *et al.* (1990) carried out a case–control study in the USA examining associations of testicular cancer with occupation and occupational exposures. Cases (n = 271) were aged 18–42 years and diagnosed between 1976 and 1981 in three medical institutions, two of which

treated military personnel, while the controls (n = 259) were men diagnosed in the same centres with a cancer other than of the genital tract. A complete occupational history was taken and participants were also asked about specific exposures, including to radar equipment and to MW radiation, MW ovens or other radio-waves. For all cancers of the testis combined, the odds ratio associated with exposure to MW radiation, MW ovens or other radio-waves was significantly increased, while the odds ratio for exposure to radar equipment was not elevated (Table 2.5). The participants were further classified by an industrial hygienist as to degree of exposure to MW radiation, MW ovens, and other radio-waves and no indication of an exposure–response relationship was found. [The Working Group noted that the exposure-classification approach was based on self-report and was probably subject to substantial misclassification.]

Baumgardt-Elms *et al.* (2002) carried out a case–control study examining the association of cancer of the testis with workplace exposures to EMF. The histologically confirmed cases (n = 269; including 170 seminomas and 99 non-seminomas) were recruited between 1995 and 1997 from five German regions (response rate, 76%). The controls (n = 797) were randomly selected from mandatory registries of residents, with matching on age and region (response rate, 57%). Occupational exposure to EMF was assessed in standardized face-to-face interviews with closed questions. For radar, job descriptions were selected for participants who had reported exposure to radar or had worked in occupations and industries involving such exposures. The participants were classified as to exposure to radar on the basis of expert review and measurements conducted in Germany. There was no excess risk of cancer of the testis associated with being classified as having exposure to radar. [A comparison of self-report of exposure with classification by the expert panel showed substantial misclassification from reliance on self-report.]

(b) Cohort study

Davis & Mostofi (1993) reported six cases of cancer of the testis in a cohort of 340 police officers who used hand-held radar guns in the state of Washington, USA. Only one case was expected, based on national data. [The Working Group noted that the finding of the six cases as a cluster had sparked the investigation. Exposure assessments were not made for the full cohort.]

2.1.5 Other cancers

Armstrong *et al.* (1994) carried out a nested case–control study of the association between exposure to PEMFs and various cancers, including lung (described in Section 2.1.1). An association was observed between exposure to PEMFs and cancer of the lung (Table 2.6). The highest excess risk was found in cases first exposed 20 years before diagnosis. [The relevance of the measured EMF parameters to exposure to RF radiation was unclear.]

No association of RF radiation with cancer of the lung has been reported in other studies (Milham, 1988a; Szmigielski, 1996; Tynes *et al.*, 1996; Lagorio *et al.*, 1997; Morgan *et al.*, 2000; Groves *et al.*, 2002; Degrave *et al.*, 2009; described in Section 2.1.1, and Table 2.6). A later overview by Szmigielski *et al.* (2001) reported an incidence rate ratio of 1.06 in the population studied by Szmigielski (1996), based on 724 not-exposed cases and 27 exposed cases.

Tynes *et al.* (1996) (described in Section 2.1.1) studied the impact of exposure to RF radiation (405 kHz to 25 MHz) in an occupational cohort of Norwegian female radio/telegraph operators who had worked at sea for extended periods. There were increased standardized incidence ratios (SIR) for cancers of the breast and uterus (Table 2.6). A nested case–control analysis for cancer of the breast was performed within this cohort. To control for the possible confounding effect of reproductive history, the investigators linked the cohort to a unique database from

the Norwegian Central Bureau of Statistics that contained information on the reproductive histories of Norwegian women born between 1935 and 1969. After adjusting for duration of employment, the odds ratio for cancer of the breast was 4.3 (95% CI, 0.7–26.0) in women aged ≥ 50 years who had performed a large amount of shift-work (> 3.1–20.7 category–years). Adjustment for shift-work and relevant reproductive history reduced the odds ratio for cancer of the breast to 1.1 (95% CI, 0.2–6.1) in those with the longest duration of employment. [The apparent excess risk of cancer of the breast in this cohort, based on high-quality databases and linkage, was not explained by reproductive history and could be potentially attributed to exposure to light at night.]

2.2 Environmental exposure from fixed-site transmitters

Ecological studies are considered to provide a lower quality of evidence than case–control or cohort studies, as they reflect the possibility of uncontrolled confounding and possible misclassification of exposure. With regard to exposure to RF radiation and its association with cancers of the brain, there appears to be little possibility of confounding by anything other than socio-demographic factors associated with diagnostic opportunity. For other cancer sites, confounding may be of greater concern.

Individual measurements of distance from a transmitter as a proxy for exposure are effectively ecological measures, in which the ecological unit includes everyone living at the same distance, or within a restricted range of distances, from the transmitter. Spot measurements will only be partly correlated with total exposure and even a personal exposure meter provides only an approximation of the dose of radiation absorbed by a specific tissue. Measurement of lifetime exposure is problematic regardless of the study design, particularly when there is a high level of population mobility and measurements of exposure are not readily available for previous areas of residence.

The crucial issue is to what extent the exposure surrogate is associated with the radiation absorbed, since this modulates the statistical power of the study. Some studies have validated correlations between proxy measures, based either purely on distance or on a more sophisticated propagation model. In some cases the correlation has been estimated at approximately 60%, in others it is < 10%, especially when based upon self-report of exposures (Schmiedel *et al.*, 2009; Viel *et al.*, 2009; Frei *et al.*, 2010). Hence it is difficult to assume that exposure classification based on distance-based proxy measurements is useful, unless validation measurements are included. Detailed modelling of field propagation shows that several parameters are potentially required.

2.2.1 Cancer of the brain

(a) Ecological studies

In several ecological studies, incidence or mortality rates of brain tumours have been compared between defined populations living close to television or radio broadcast stations or other RF radiation fixed-site transmitters or transmission towers.

Selvin *et al.* (1992) undertook a cross-sectional analysis in which the proportion of people aged < 21 years with cancer of the brain diagnosed between 1973 and 1978 living ≤ 3.5 km or > 3.5 km from a large MW transmission tower (Sutro Tower) in San Francisco, USA (n = 35) was compared with corresponding proportions from the 1980 USA census. The odds ratio for cancer of the brain and living ≤ 3.5 km from the tower was 1.16 [95% CI, 0.56–2.39]. [No possible confounding factors were considered, nor were the ambient levels of RF radiation in the compared areas documented.]

Table 2.4 Case–control study of uveal melanoma and occupational exposure to radiofrequency radiation

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stang *et al.* (2001) Germany, 1995–98	118 (37/81)	475	Population-based study: 327 controls sampled and matched from the same region of residence, age, and sex. Hospital-based study: controls were 148 patients with benign intraocular tumours.	Interviewer-administered structured questionnaire	Uveal melanoma	Radar units	1	0.4 (0.0–2.6)	Age, sex, region, SES, colour of iris and hair	Results of the population-based study (37 cases) and the hospital-based study (81 cases) were pooled.
						Radio set:				
						Ever exposed	9	3.3 (1.2–9.2)		
						Exposed ≥ 5 yr before	9	3.3 (1.2–9.2)		
						Exposed for ≥ 3 yr	7	2.5 (0.8–7.7)		

SES, socioeconomic status; yr, year

Table 2.5 Case–control studies of cancer of the testis and occupational exposure to radiofrequency radiation

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hayes *et al.* (1990) USA, 1976–81	271	259	Non-genital cancer, diagnosed in same hospital	Interviews, including a complete occupational history. Participants were queried on specific exposures including radar equipment and MW radiation, MW ovens or other radio-waves. In-person interviews were held in the hospital with 69% of the cases and with 71% of the controls, and over the telephone at home with the rest of the cases and controls.	Testicular seminoma (n = 60) Other germinal (n = 206) Non-germinal (n = 5)	*Radar equipment*			Age	Self-reported exposure Two of the three centres treated military personnel Poor agreement between self-reporting and job title No response rates reported
						Seminoma	12	1.3 (0.6–2.8)		
						Other	30	1.1 (0.6–1.9)		
						Total	NR	1.1 (0.7–1.9)		
						Other MW/RF				
						Seminoma	7	2.8 (0.9–8.6)		
						Other	24	3.2 (1.4–7.4)		
						Total	NR	3.1 (1.4–6.9)		
						Based on job title:				
						None	116	1.0		
						Low	10	2.3 (0.6–9.4)		
						Medium	6	1.0 (0.3–3.8)		
						High	12	0.8 (0.3–2.0)		

Table 2.5 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Baumgardt-Elms *et al.* (2002) Germany, 1995–97	269	797	Controls were randomly selected from mandatory registries of residents, and matched on age and region (response, 57%).	Interviewer-administered standardized questionnaire	Testicular (170 seminoma and 99 non-seminoma)	*Radar units*	22	1.0 (0.60–1.75)		Exposure to RF weighted by duration and distance from source
						RF emitters	50	0.9 (0.60–1.24)		
						Radar units				
						0	251	1.0		
						> 0 to ≤ 45	7	1.4 (0.55–3.77)		
						> 45 to ≤ 135	4	0.5 (0.17–1.55)		
						> 135 to ≤ 2225	7	0.9 (0.36–2.19)		
						RF emitters				
						0	220	1.0		
						> 0 to ≤ 6	19	1.0 (0.56–1.74)		
						> 6 to ≤ 15	14	0.7 (0.38–1.35)		
						> 15 to ≤ 102	16	0.9 (0.46–1.56)		

MW, microwave; NR, not reported; RF, radiofrequency radiation

Table 2.6 Cohort studies of cancers of the lung and other sites and occupational exposure to radiofrequency radiation

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Milham (1988a, b) USA	67 829	1979–84	Licensing as an amateur radio operator	Cancer of the respiratory system (160–163)	None	209	SMR, 0.66 (0.58–0.76)		The death rates used to estimate the expected numbers were not specified
Armstrong *et al.* (1994) Canada and France	191 749	1970–89	Exposures assessed through a job-exposure matrix based on about 1000 person-wks of measurements from exposure meters worn by workers to derive estimates of short-duration PEMFs, or high-frequency transient fields.	Lung cancer (162)	*PEMFs* < Median > Median ≥ 90th percentile First exposed 0–20 yr before diagnosis: < Median > Median ≥ 90th percentile First exposed > 20 yr before diagnosis: < Median > Median ≥ 90th percentile	 200 308 84 198 273 67 78 128 27	OR 1.00 1.27 (0.96–1.68) 3.11 (1.60–6.04) 1.00 1.48 (1.08–2.03) 1.80 (1.13–4.30) 1.00 3.83 (1.45–10.10) 7.02 (1.77–27.87)	SES	Nested case–control analysis Controls for each case were selected at random from the cases risk set and matched to the case by utility and year of birth. Exposure was counted only up to the date of diagnosis of the case.
Szmigielski (1996) Poland	Average of 127 800 men, yearly during 15 yr	1971–85	Military safety (health and hygiene) groups classified military service posts as having exposure, or not, to RF	Cancer of the larynx and lung	*Occupational exposure to RF* Not exposed Exposed	 [420]* [13]*	*Incidence rate ratios* 1.00 1.06 (0.72–1.56)	None specified	Cross-sectional study.
Tynes *et al.* (1996) Norway	2619 women	1961–91	Radio and telegraph operators with potential exposure to RF and ELF fields	Lung (ICD-7 code 162) Breast (ICD-7 code 170) Uterus (ICD-7 code 172)	*Potential exposure* Lung Breast Uterus	 5 50 12	*SIR* 1.2 (0.4–2.7) 1.5 (1.1–2.0) 1.9 (1.0–3.2)	Age, time since certification, calendar year, age at first childbirth	Women certified as radio and telegraph operators 1920–80

Table 2.6 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Lagorio *et al.* (1997) Italy	481 women	1962–92	Occupational history from plant records. RF generated by dielectric heat sealers. Exposure of 10 W/m^2 equivalent power-density frequently exceeded.	Lung (162)	*Job title*		*SMR*	Sex, age, calendar period-specific regional person-yr at risk	Mortality analysis; restricted to women
					RF-sealer operators	1	[5 (1.27–27.85)]*		
					Other workers	0	-		
					All female workers	1	[3.3]*		
Morgan *et al.* (2000) USA	195 775	1976–96	Job-exposure matrix, developed through expert consultation that categorized each of 9724 job titles into different RF exposure groups: background, low, moderate, and high, corresponding roughly to < 0.6 W, 0.6 to < 2.0 W, 2.0 to < 5.0 W, 5.0 to < 50 W and ≥ 50 W, respectively.	Respiratory system cancer	*RF exposure*		*SMR*	Age, sex, and race for external comparisons; and age, sex, and period of hire for internal comparisons	All employees of Motorola; exposure from cellular phones not assessed. Definition of exposure categories unclear
					High and moderate	94	[approx. 0.8]*		

Table 2.6 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Groves *et al.* (2002) USA	40 581 men (271 women excluded)	1950–97	United States Navy personnel with potential for RF exposure; job classified as having low or high exposure by a consensus of Navy personnel involved in training and operation	Trachea, bronchus and lung (162)	*Job-associated exposure to RF*		*SMR*	Age at cohort entry and attained age	White United States Navy (male) veterans of Korean War (1950–54) Reference: all white men, USA
					Low	497	0.87 (0.79–0.94)		
					High	400	0.64 (0.58–0.70)		
Degrave *et al.* (2009) Belgium	Military personnel (4417 men) in batallions equipped with radar, and 2932 controls.	1968–2003	Exposure levels on the site where the battalion lived and worked were characterized; individual exposure assessment could not be conducted.	Respiratory and intra-thoracic organs (160–169)	Control cohort Radar exposed	28 45	1.00 1.07 (0.66–1.71)		Cause of death found for 71% of the men in the radar group and 70% in the control group.

* Values calculated/deduced by the Working Group

ELF, extremely low frequency electric and magnetic field; MW, microwaves; OR, odds ratio; PEMFs, pulsed electromagnetic fields; RF, radiofrequency radiation; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; W, watt; V, volt; wk, week; yr, year

Hocking *et al.* (1996) studied incidence and mortality attributable to cancer of the brain (ICD-9 code 191) near three television and FM-radio broadcasting antennae located close together in Sydney, Australia. Exposure from these towers was to amplitude modulation (AM) at 100 kW and frequency modulation (FM) at 10 kW for signals at 63–215 MHz. Calculated power densities of RF radiation ranged from 8.0 μW/cm^2 near the tower to 0.2 μW/cm^2 at a distance of 4 km and 0.02 μW/cm^2 at 12 km. For cancer of the brain at all ages in three "inner ring" municipalities relative to six "outer-ring" municipalities, the rate ratio for incidence was 0.89 (95% CI, 0.71–1.11; 740 cases) and the rate ratio for mortality was 0.82 (95% CI, 0.63–1.07; 606 deaths). [Municipality-specific incidence rates were only available in broad, sex-specific age groups: 0–14, 15–69 and ≥ 70 years]. For children aged 0–14 years, the corresponding rate ratios were 1.10 (95% CI, 0.59–2.06; 64 cases) and 0.73 (95% CI, 0.26–2.10; 30 deaths). All municipalities were said to have upper middle-class populations.

Prompted by reported clustering of leukaemia and lymphoma near a high-power television and FM-radio broadcast antenna in the West Midlands, England, Dolk *et al.* (1997a) studied the incidence of cancer within a radius of 10 km from the antenna. The authors noted that available field-strength measurements generally showed a decrease of the average field strength with increasing distance from the transmitter, although with undulations in predicted field strength up to about 6 km from the transmitter. The maximum total power-density equivalent summed across frequencies at any one measurement point was 0.013 W/m^2 for television, and 0.057 W/m^2 for FM radio. Observed numbers of cases within 0–2 km and 0–10 km of the antenna were compared with "national" incidence rates, adjusted for age, sex, year and deprivation quintile (calculated based on data on unemployment, overcrowding, and social class of head of household). For all tumours of the brain (ICD-8/ICD-9 codes 191, 192, 225, and ICD-9 codes 237.5, 237.6, 237.9) in persons aged ≥ 15 years, the SIR was 1.29 (95% CI, 0.80–2.06) within 0–2 km and 1.04 (95% CI, 0.94–1.16) within 0–10 km. For malignant tumours of the brain only, these SIRs were 1.31 (95% CI, 0.75–2.29) and 0.98 (95% CI, 0.86–1.11), respectively.

Dolk *et al.* (1997b) undertook a similar analysis of cancer incidence in proximity to all 20 other high-power radio and television transmitter antennae in the United Kingdom. [With one exception, information about field distribution and strength in proximity to those antennae was not provided.] In this analysis, results for tumours of the brain were reported only for children aged 0–14 years and in proximity to all 21 such antennae (including that studied by Dolk *et al.*, 1997a). At 0–2 km from the antenna, SIRs were 0.62 (95% CI, 0.17–1.59) for all tumours of the brain and 0.50 (95% CI, 0.10–1.46) for malignant tumours, while at 0–10 km SIRs were 1.06 (95% CI, 0.93–1.20) and 1.03 (95% CI, 0.90–1.18), respectively.

Ha *et al.* (2003) studied the incidence of cancer between November 1993 and October 1996 in people aged ≥ 10 years in populations of 11 administrative areas of the Republic of Korea within about 2 km of high-power (≥ 100 kW) AM transmitter antennae, 31 such areas within about 2 km of low-power AM transmitter antennae (50 kW), and 4 control areas near, but not within 2 km, of each high-power transmitter antenna (44 control areas in total). Incident cases of cancer were ascertained from medical insurance records [no information was given regarding the completeness and accuracy of these records]. Directly age-standardized incidence rate ratios for cancer of the brain (ICD-9 codes 191–192, and ICD-10 codes C70–C72) comparing people living near high-power transmitter antennae with people living near low-power antennae were 1.8 (0.9–11.1) in males and females combined. Indirectly age-standardized incidence rate

ratios for cancer of the brain comparing people living near high-power transmitter antennae at different levels of power output with those in control areas were 2.27 (95% CI, 1.30–3.67) for a power output of 100 kW, 0.86 (95% CI, 0.41–1.59) for 250 kW, 1.47 (95% CI, 0.84–2.38) for 500 kW, and 2.19 (95% CI, 0.45–6.39) for 1500 kW.

Park *et al.* (2004) reported the results of a similar study of cancer mortality in 1994–95 in people of all ages in the Republic of Korea. Mortality rates within an area of 2 km surrounding AM broadcasting towers with a power of > 100 kW were compared with those in control areas that had a similar population and were located in the same province as the matched exposed area. Information on deaths due to cancer was identified in Korean death certificates from 1994 to 1995. The resident population at that time was assumed to correspond to that recorded in the nationwide population census of 1990. To control for possible selection bias, four control areas (n = 40) were matched to each exposed area (n = 10). Based on six age groups, annual age-adjusted world population-standardized mortality rates were calculated per 100 000 residents. Mortality rate ratios (MRR) were calculated comparing 10 areas within about 2 km of high-power antennae with 40 areas situated > 2 km from high-power antennae in the same or neighbouring provinces. The directly standardized MRR for cancer of the CNS, comparing areas near high-power antennae with control areas, was 1.52 (95% CI, 0.61–3.75).

The incidence of cancer in relation to mobile-phone base-station coverage was investigated in 177 428 people living in 48 municipalities in Bavaria, Germany, between 2002 and 2003 (Meyer *et al.*, 2006). Municipalities were classified on a crude three-level exposure scale based on the operating duration of each base station and the proportion of the population living within 400 m of the base station. Based on 1116 malignant tumours in 242 508 person–years, no indication of an overall increase in the incidence of cancer was found in the populations of municipalities belonging to the highest exposure class. The Potthoff-Whittinghill test was used to examine the homogeneity of the case distribution among the communities. The following cancers were not found to be heterogeneously distributed: breast (P = 0.08); brain and CNS (P = 0.17); and thyroid (P = 0.11). For leukaemia, there were indications of underreporting and thus the test for homogeneity was not performed. [The exposure assessment in this study was very crude and likely to result in substantial random exposure misclassification. The number of organ-specific tumours was not reported, but is expected to be small given the total number of tumours. Thus, the observed absence of an association may be real, or due exposure misclassification, or to inadequate statistical power.]

(b) Case–control studies

Schüz *et al.* (2006b) reported on the association of proximity of a DECT (Digital Enhanced Cordless Telecommunications) cordless-phone base station to a person's bed (a proxy for continuous low-level exposure to RF radiation during the night) with the risk of brain glioma and mengioma in a case–control study in Germany that was a component of the INTERPHONE study. This was a subanalysis of the main study in which no association of either brain glioma or meningioma with use of cordless phones had been found (Schüz *et al.*, 2006a). Cases were newly diagnosed with a histologically confirmed glioma or meningioma in 2000–03, aged 30–69 years, lived in the study region, had a main residence in the study region, and had a knowledge of German sufficient for interview. Proxy interviews were conducted if the cases or controls had died or were too ill for interview. Controls were selected randomly from compulsory population registers in the study regions, were required to meet relevant case-inclusion criteria, and were initially frequency-matched to the cases by age, sex and region. Participation rates were: patients

with glioma, 79.6%; patients with meningioma, 88.4%; and controls, 62.7%. Interview questions about cordless phones addressed the type of phone (DECT or analogue), make and model, the dates on which use started and stopped, and the location of the base station within the residence. Since many subjects could not recall whether their cordless phone was a DECT phone, information on the make, model and price of the phone and its technical features were used to classify phones into "definitely" or "possibly" DECT, or definitely analogue. Participants were considered definitely or possibly exposed if, in addition, the DECT base station was located 3 m or less from the bed (this was the case for 1.6% of participants). Information from proxy interviews (patients with glioma, 10.9%; patients with meningioma, 1.3%; and control participants, 0.4%) was used in the analysis, since most proxies lived with their index subjects and were users of the same cordless phones. For analysis, controls were individually matched 2 : 1 to cases by birth year, sex, region and date of diagnosis (case) or interview (control); 366 cases of glioma and 381 cases of meningioma were analysed. Risk of glioma or meningioma was not increased with definite or possible exposure to DECT base stations; nor was there any consistent trend with time since first exposure (Table 2.7). [This study was limited by the small proportion of people who were considered to be exposed, difficulty in classifying cordless phones as DECT or analogue, and lack of associated consideration of other sources of exposure to RF radiation.]

Ha *et al.* (2007) reported on risk of childhood cancers of the brain in relation to residential exposure to RF radiation from AM-radio fixed-site transmitters (power, > 20 kW) in the Republic of Korea. Cases were diagnosed with cancer of the brain (ICD-9 codes 191–192, and ICD-10 codes C70–C72) between 1993 and 1999, and controls were diagnosed over the same period with a respiratory disease (ICD-9 codes 469–519, and ICD-10 codes J20 and J40–J46). Both cases and controls were identified through the national health insurance system of the Republic of Korea, and individually matched by age, sex and year of first diagnosis. Both were restricted to children diagnosed at one of fourteen large cancer or tertiary-care hospitals. Cancer diagnoses were confirmed by reference to the national cancer registry or hospital medical records [the basis for confirmation was not stated]. Cases were excluded if the diagnosis of cancer could not be confirmed; controls were excluded if they had a history of cancer recorded in the national cancer registry (which was 80% complete in 1998); and both were excluded if they had incomplete addresses (which were obtained from the medical records). The distance from each subject's residence to the nearest AM-radio transmitter established before diagnosis was evaluated by means of a geographical information system, and total exposure to RF radiation from all AM-radio fixed-site transmitters was estimated with a flat-earth attenuation statistical-prediction model, which took into account features of the receiving point and the propagating pathway [intervening terrain, the output power of the fixed-site transmitters and their distance from the receiving point]. The prediction program was validated by taking measurements of field strength at sites around 11 fixed-site transmitters, and correction coefficients were calculated and applied to the prediction program. Twenty-nine of the thirty-one radio fixed-site transmitters were established between 1980 and 1995, and children in the study were born between 1978 and 1999. Socioeconomic status was classified according to the number of cars owned per 100 people in defined regions and population density in these regions was used as a surrogate for industrialization and environmental pollution. The odds ratio for cancer of the brain was not materially increased in those living closest (≤ 2 km) to a transmitter (OR, 1.42; 95% CI, 0.38–5.28) or in those with greatest estimated exposure (≥ 881 mV/m) to RF radiation (OR, 0.77; 95% CI, 0.54–1.10) (Table 2.7). [This

Table 2.7 Case–control studies of cancer of the brain and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Schüz *et al.* (2006b) Bielefeld, Heidelberg, Mainz, Mannheim, Germany, 2000–03	747	1494	Population	Interviewer-administered questionnaire	Brain (glioma and meningioma)	*DECT cordless-phone base station ≤ 3m from bed*			Covariates: age, sex, region, educational level
						Glioma			
						Definitely			
						No	342	1.00	
						Yes	3	0.50 (0.14–1.76)	
						Possibly or definitely			
						No	342	1.00	
						Yes	5	0.82 (0.29–2.33)	
						Time since first exposure (possibly or definitely)			
						No, < 1 yr	342	1.00	
						1–4 yr	3	0.95 (0.24–3.70)	
						≥ 5 yr	2	0.68 (0.14–3.40)	
						Meningioma			
						Definitely			
						No	360	1.00	
						Yes	5	1.09 (0.37–3.23)	
						Possibly or definitely			
						No	364	1.00	
						Yes	5	0.83 (0.29–2.36)	
						Time since first exposure (possibly or definitely)			
						No, < 1 yr	364	1.00	
						1–4 yr	1	0.33 (0.04–2.80)	
						≥ 5 yr	4	1.29 (0.37–4.48)	

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Ha *et al.* (2007) Republic of Korea, 1993–99	956	1020	Hospital-based study. Controls had attended one of 14 large cancer or tertiary care hospitals where the cases had been diagnosed, for management of respiratory disease (ICD-9 469–519; ICD-10 J20 and J40–46). Controls were individually matched to a case by age, sex, and year of first diagnosis.	Based on locations of 31 AM transmitters of ≥ 20 kW and 49 associated antennae and locations of subjects' residences at time of diagnosis.	Brain (ICD-9 code 191–192; ICD-10 codes C70–C72)	*Distance from nearest AM radio-transmitter established before subject's year of diagnosis (km)*	All brain cancer (age < 15 yr)		Children aged < 15 yr. The use only of large hospitals for ascertainment of controls could mean that controls are not representative of population from which cases were drawn. Covariates: age, sex, residential location, population density, SES
						≤ 2	10	1.42 (0.38–5.28)	
						> 2–4	32	1.40 (0.77–2.56)	
						> 4–6	59	1.02 (0.66–1.57)	
						> 6–8	90	1.08 (0.73–1.59)	
						> 8–10	114	0.94 (0.67–1.33)	
						> 10–20	244	1.01 (0.77–1.34)	
						> 20	400	1.00 (reference)	
						Unknown	7	4.30 (0.50–36.73)	
						P (trend)		0.76	
						Total exposure to RF (mV/m)			
						< 532.55*	329	1.00 (reference)	*Quartiles of the distribution
						532.55 – < 622.91	185	0.66 (0.47–0.92)	
						622.91 – < 881.07	181	0.72 (0.51–1.01)	
						≥ 881.07	254	0.77 (0.54–1.10)	
						P (trend)		0.73	

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Ha *et al.* (2007) (cont.)						*Distance from nearest AM radio-transmitter established before subject's year of diagnosis (km)*	All brain cancer (age < 1 yr)		
						≤ 10	10	0.41 (0.05–3.10)	
						> 10–20	10	0.49 (0.06–3.80)	
						> 20	12	1.00 (reference)	
						P (trend)		0.78	
						Total exposure to RF (mV/m)			
						< 485.85*	9	1.00 (ref.)	
						485.85 – < 632.96	7	3.56 (0.49–25.95)	
						632.96 – < 810.81	7	1.41 (0.12–17.11)	
						≥ 810.81	9	5.13 (0.44–60.26)	
						P (trend)		0.27	
Oberfeld (2008) Hausmannstätten & Vasoldsberg, Austria, 1984–97									The status of this study (printed version, German and English online versions) is controversial. It was therefore decided to remove the description of this study from text and tables.

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Spinelli *et al.* (2010) Western Provence-Alpes-Côte d'Azur (PACA), France, 2005	122	122	Hospital-based	Self-administered questionnaire and face-to-face interview, including lifetime job history, job title, dates, tasks	Brain (glioma grades II–IV)	*Residence within 500 m of:*			Covariates: age, sex
						Cell-phone tower	19	0.49 (0.26–0.92)	
Elliott *et al.* (2010) United Kingdom, 1999–2001	251	1004	Population-based study. Controls were children aged < 4 yr, individually matched to cases by sex and date of birth.	Location of birth residence relative to nearby macro-cell mobile-phone base stations; distance to nearest base station; total power output of all base-stations within 700 m; modelled power density at birth address	Brain and CNS (ICD-10 codes C71–C72)	*Distance from nearest macro-cell mobile-phone base-station*			Covariates: percentage of population with education to degree level or higher, Carstairs score (a composite area-deprivation measure), population density, and population mixing (percentage immigration into the area over the previous year).
						Lowest third	85	1.00	
						Intermediate third	85	0.95 (0.67–1.34)	
						Highest third	81	0.95 (0.65–1.38)	
						For 15th to 85th centile increase (continuous measure)	251	1.12 (0.91–1.39)	
						Total mobile-phone frequency power-output (kW)			
						No base station within 700 m	150	1.00	
						Lower half	56	1.02 (0.72–1.46)	
						Upper half	45	0.83 (0.54–1.25)	
						For 15th to 85th centile increase (continuous measure)	251	0.89 (0.73–1.09)	

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Elliott *et al.* (2010) (contd.)						*Modelled mobile-phone frequency power density (dBm)*			
						Lowest third	93	1.00	
						Intermediate third	80	0.97 (0.69–1.37)	
						Highest third	78	0.76 (0.51–1.12)	
						For 15th to 85th centile increase (continuous measure)	251	0.82 (0.55–1.22)	

AM, amplitude modulation (radio); CNS, central nervous system; DECT, Digital Enhanced Cordless Telecommunications; kW, kilowatt; NMT, Nordic Mobile Telephone (standard); RF, radiofrequency radiation; SES, socioeconomic status; yr, year

study was limited by the lack of a clear population base, possible mismatch between the population sampled for cases and that sampled for controls, and the lack of a cumulative measure of exposure to RF radiation that took into account variation in an individual's place of residence between birth and diagnosis of cancer or respiratory disease.]

[Oberfeld (2008): the status of this study (printed version, German and English online versions) is controversial. It was therefore decided to remove the description of this study from text and tables.]

Spinelli *et al.* (2010) undertook a pilot case–control study of newly diagnosed, histopathologically confirmed malignant primary tumours of the brain (defined as previously untreated glioma, grades II–IV) in people aged ≥ 18 years treated in the two principal referral hospitals for cancer of the brain in the west of the Provence-Alpes-Côte d'Azur (PACA) region in France. Controls were other patients in the neurosurgery department who were hospitalized for reasons other than cancer (mainly herniated intervertebral disc, intracranial aneurysm, trauma, and epidural haematoma) who were individually matched to cases by age, sex and residence in the west of PACA. Participants completed a self-administered questionnaire and were interviewed by an occupational physician at the hospital they attended within 3 months after surgery; the physician also checked their questionnaire. [It was not stated whether the interviewer was blind to the case or control status of participants.] Family members also helped with self-administered questionnaires, more often for cases than controls. Proxy interviews were completed for 2% of cases. Occupational exposures were the principal focus of the questionnaire and interview, but participants were also asked about use of mobile phones and residence in proximity to a mobile-phone tower. Information was obtained from 75.3% of cases [the participation rate of controls was not stated]. Nineteen cases and thirty-three controls reported a mobile-phone tower within 500 m of their residence (age- and sex-adjusted OR, 0.49; 95% CI, 0.26–0.92) (Table 2.7). [This study was limited by its small size and because it was hospital-based. The participation rate for controls was not stated and it is likely that people prone to serious injury were over-represented among the controls. The interviewer may not have been blind to the case or control status of participants. Specific questions regarding proximity of residence to mobile-phone towers were not described and may have been highly prone to recall error, and there were few participants with occupational exposure to RF radiation.]

Elliott *et al.* (2010) undertook a case–control study of early childhood cancer in the United Kingdom based on all cases of cancer in children aged 0–4 years registered in 1999–2001. Of 1926 registered cases, the geographical coordinates of addresses at birth, and exposure based on the birth address were available for 1397 children (73%). Of the latter, 251 had cancers of the brain and CNS (ICD-10 codes C71–C72). For each case, four controls from the national birth register, with complete birth addresses and individually matched to cases by sex and date of birth (5588 controls), were obtained from 6222 originally randomly selected (90%). The four national mobile-phone operators provided detailed data on all 76 890 macro-cell base stations operating in 1996–2001. Three exposure measures for the birth address of each case and control were obtained: the distance from the nearest macro-cell mobile-phone station; the total power output (kW) from summation across all base stations within 700 m; and computed modelled power density (dBm) at each birth address for base stations within 1400 m. Exposures beyond 1400 m were considered to be at background levels. Measurements from field campaigns in a rural and an urban area were used to set parameter values in the power-density model. The models were validated with data from two further surveys and power-density measurements from 620 locations

across the country. Spearman's correlation coefficients between measured power density and the exposure measures were: 0.66 with modelled power density, 0.72 with distance from nearest base station, and 0.66 with total power output. The exposure measures estimated at each birth address were averaged across monthly estimates for the assumed 9 months of the pregnancy in each case. Each exposure measure was divided into thirds of the distribution across all cases and controls except for total power output, which was zero for 58% (no base station within 700 m), with the remaining 42% in two halves of their distribution. Exposure measures were fitted to models as continuous variables as well as in the above categories. Neither unadjusted nor partly or fully adjusted odds ratios suggested that risk of childhood cancer of the brain increased with increasing exposure to RF radiation from nearby macro-cell mobile-phone base stations (Table 2.7). [This study was limited by the fact that estimation of exposure was confined to the gestational period; application of birth address to the whole of gestation was assumed; and ecologically measured possible confounding variables were used to apply to individual subjects.]

(c) Cohort studies

No data were available to the Working Group.

2.2.2 Leukaemia and lymphoma

(a) Ecological studies

See Table 2.8

Hocking *et al.* (1996) published a study comparing incidence of and mortality from leukaemia during 1972–90 in nine municipalities, three of which were located around television towers and six that were more distant. Increased rate ratios for incidence (IRR, 1.24; 95% CI, 1.09–1.40) and mortality (MRR, 1.17; 95% CI, 0.96–1.43) for leukaemia at all ages were obtained and generally higher rate ratios were seen for childhood leukaemia (IRR, 1.58; 95% CI, 1.07–2.34; MRR, 2.32; 95% CI, 1.35–4.01) than for leukaemia at all ages, comparing the three "inner ring" municipalities with six "outer ring" municipalities. A more marked association was observed between proximity to television towers and mortality (MRR, 2.4; 95% CI, 1.4–3.7) than incidence (IRR, 1.8; 95% CI, 1.2–2.5) from leukaemia. [No individual measurements were undertaken and main analyses could only be adjusted for covariates by group-level (aggregated) data.]

In 1997, Dolk *et al.* published two studies on cancer incidence during 1974–86. The first was a study in a small area in response to an unconfirmed report of a cluster of leukaemias and lymphomas near the Sutton Coldfield television and radio-transmitter in the West Midlands, England (Dolk *et al.*, 1997a). The second, to place in context the findings of the Sutton Coldfield study, was carried out near 20 high-power television and radio-transmitters in the United Kingdom (Dolk *et al.*, 1997b). In the Sutton Coldfield study, an increased risk of leukaemia in adults was found when the observed and expected numbers of cases (derived from national incidence rates) were compared (observed/expected, 1.83; 95% CI, 1.22–2.74) within 2 km of the transmitter and there was a decline in risk with distance (Stone's P value = 0.001). The latter was tested by use of 10 bands of increasing distance from the transmitter within a circle with a radius of 10 km around it. The findings appeared to be consistent between 1974 and 1980, and 1981 and 1986. For NHL, a suggestion of a decrease in risk was seen within the 2 km area (observed/expected, 0.66; 95% CI, 0.28–1.30) while for the total study area of 0–10 km, risk appeared to be increased (observed/expected, 1.23; 95% CI, 1.11–1.36). In the second study, covering the United Kingdom (Dolk *et al.*, 1997b), evidence of a decline in risk of leukaemia was found with increasing distance from the transmitter (Stone's P value = 0.05); however, the magnitude (at 0–10 km: observed/expected, 1.03; 95% CI, 1.00–1.07) and the pattern

Table 2.8 Ecological studies of leukaemia and lymphoma and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Hocking *et al.* (1996) Australia	585 000	1972–90	Residential proximity to TV towers	Leukaemia (204–208)	Overall rate ratios for incidence and mortality, respectively, inner and outer residential area compared.	1206/847	Incidence, 1.24 (1.09–1.40) Mortality, 1.17 (0.96–1.43)	Age, sex, calendar period	Reference population: whole of New South Wales
					Inner area *vs* ref. population	33	Childhood SIR, 1.8 (1.2–2.5)		
					Outer area *vs* ref. population	101	Childhood SIR, 1.1 (0.9–1.4)		
					Inner area *vs* ref. population	19	Childhood SMR 2.4 (1.4–3.7)		
					Outer area *vs* ref. population	40	Childhood SMR 1.0 (0.7–1.4)		
Dolk *et al.* (1997a) United Kingdom	Around 408 000	1974–86	Distance to Sutton Coldfield radio and TV transmitter	Haemato-poietic and lymphatic cancers (200–202; 203 + 238.6; 204–208)	Distance 0–2 km Distance 0–10 km Stone's *P*-value	45 935	1.21 (0.91–1.62) 1.04 (0.98–1.11) Unconditional $P = 0.153$	Region	Observed/expected ratios and Stone's *P*-value are given for persons aged ≥ 15 yr, stratified by age, sex, year, and SES. Declining risk with increasing distance was seen only for all leukaemias.
				Leukaemia (204–208)	Distance 0–2 km Distance 0–10 km Stone's *P*-value	23 304	1.83 (1.22–2.74) 1.01 (0.90–1.13) Unconditional $P = 0.001$ Conditional $P = 0.001$		
				NHL	Distance 0–2 km Distance 0–10 km Stone's *P* value	8 357	0.66 (0.28–1.30) 1.23 (1.11–1.36) Unconditional $P = 0.005$ Conditional $P = 0.958$		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Dolk *et al.* (1997b) United Kingdom	Around 3 390 000	1974–86	Distance to radio and television transmitters in the United Kingdom (excluding Sutton Coldfield)	Leukaemia (204–208)	Distance 0–2 km Distance 0–10 km Stone's *P* value	79 3 305	0.97 (0.78–1.21) 1.03 (1.00–1.07) Unconditional *P* = 0.001 Conditional *P* = 0.052	Region	Observed/expected ratios and Stone's *P* value are given for persons aged ≥ 15 yr, stratified by age, sex, year, and SES.
Cooper *et al.* (2001) United Kingdom	NR	1987–94	Distance to Sutton Coldfield television transmitter	Leukaemia (204–208)	Distance from transmitter: 0–2 km, all ages, all persons 0–10 km, all ages, all persons Stone's *P* values, all ages, all persons 0–2 km, age 0–14 yr, all persons 0–10 km, age 0–14 yr, all persons Stone's *P* values, age 0–14 yr, all persons	 20 333 1 26 	 1.32 (0.81–2.05) 1.16 (1.04–1.29) Unconditional *P* = 0.038 Conditional *P* = 0.409 1.13 (0.03–6.27) 1.08 (0.71–1.59) Unconditional *P* = 0.420	-	Observed/expected ratios and Stone's *P* values (unconditional and conditional) are given. Stratified by age, sex, and social deprivation. Results for other haematopoietic cancers are reported in the manuscript.

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Michelozzi *et al.* (2002) Italy	49 656	1987–99	Distance to Vatican radio station, Rome	Leukaemia (204–208)	Distance from radio station (km), (cumulative areas)			Deprivation index	
					Total (age > 14 yr)		*SMR*		
					0–2	2	1.8 (0.3–5.5)		
					0–4	11	1.5 (0.8–2.6)		
					0–6	23	1.2 (0.8–1.8)		
					0–8	34	1.2 (0.8–1.6)		
					0–10	40	1.1 (0.8–1.4)		
					P, Stone's conditional test		0.14		
					Children (age 0–14 yr)		*SIR*		
					0–2	1	6.1 (0.4–27.5)		
					0–4	3	2.9 (0.7–7.6)		
					0–6	8	2.2 (1.0–4.1)		
					0–8	8	1.5 (0.7–2.7)		
					0–10	8	1.2 (0.6–2.3)		
					P, Stone's conditional test		0.036		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Ha *et al.* (2003) Republic of Korea	From 3 152 to 126 523 persons per area (total not given)	1993–96	Distance ≤ 2 km from AM transmitter	Leukaemia (204–208)	*High-power (≥ 100 kW) vs low-power (50 kW) transmitter sites:*		*Rate ratio*	Age	Rate ratios (RR) and observed/expected (O/E) ratios are given For all cancers combined: RR, 1.2 (95% CI, 1.1–1.4) for high- *vs* low-power transmitters
					Men	8.3/6.8 per 100 000 person-yr	1.2 (0.5–5.3)		
					Women	8.7/4.6 per 100 000 person-yr	1.9 (0.8–8.7)		
					Total	8.5/5.7 per 100 000 person-yr	1.5 (0.7–6.6)		
					Transmitter power of sites:		*O/E*		
					100 kW	9	1.20 (0.55–2.28)		
					250 kW	12	2.45 (1.27–4.29)		
					500 kW	10	0.65 (0.31–1.19)		
					1500 kW	4	4.26 (1.16–10.89)		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Ha *et al.* (2003) (contd.)				Malignant lymphoma (200–202)	*High-power (≥ 100 kW) vs low-power (50 kW) transmitter sites:*		*Rate ratio*		
					Men	10.5/7.1 per 100 000 person-year	1.5 (0.7–8.6)		
					Women	8.7/7.1 per 100 000 person-year	1.2 (0.6–5.6)		
					Total	9.6/7.1 per 100 000 person-year	1.4 (0.6–7.0)		
					Transmitting power of sites:		*O/E*		
					100 kW	9	1.10 (0.51–2.10)		
					250 kW	13	1.28 (0.68–2.19)		
					500 kW	16	0.98 (0.56–1.59)		
					1 500 kW	1	0.44 (0.01–2.48)		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Park *et al.* (2004) Republic of Korea	8 115 906 (of whom 1 234 123 in exposed area)	1994–95	Regions including AM-radio broadcasting towers of > 100 kW	Leukaemia (ICD-10 codes C90–95), including multiple myeloma	Total exposed *vs* control (unexposed)	55	1.70 (0.84–3.45)	Age	Direct standardized MRRs are given
					Males	33	1.89 (0.75–4.75)		
					Females	22	1.55 (0.52–4.68)		
					Age (yr)				
					0–14	11	2.29 (1.05–5.98)		
					15–29	11	2.44 (1.07–5.24)		
					30–44	9	2.16 (0.95–4.04)		
					45–59	5	0.73 (0.48–2.89)		
					60–74	10	0.87 (0.57–2.78)		
					≥ 75	6	3.08 (0.95–6.59)		
				Malignant lymphoma (ICD-10 codes C81–88)	Total exposed *vs* control (unexposed)	31	1.60 (0.72–3.56)		
					Males	19	1.52 (0.56–4.14)		
					Females	12	1.80 (0.48–6.71)		
					Age (yr)				
					0–14	1	2.46 (0.07–82.66)		
					15–29	2	1.51 (0.15–15.18)		
					30–44	5	1.94 (0.37–10.20)		
					45–59	8	1.76 (0.43–7.15)		
					60–74	13	1.41 (0.47–4.14)		
					≥ 75	2	0.55 (0.05–5.67)		

AM, amplitude modulation (radio); kW, kilowatt; MRR, mortality rate ratio; NR, not reported; O/E, observed/expected; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TV, television; *vs*, versus; yr, year

of risk seen in the Sutton Coldfield study could not be replicated. Most notably, in the second, nationwide study no increase in risk was seen nearest (within 2 km) the transmitters.

In a letter to the editor, Cooper *et al.* (2001) published updated results on adult and childhood leukaemia (1987–94) near the Sutton Coldfield transmitter. To investigate risk according to distance, the authors defined the study area as a series of 10 concentric circles around the Sutton mast and calculated the expected number of cases (by numbers, child/adult and sex) for each of the circles and for different cancer sites. Most results for childhood cancers gave no evidence of a decline in the ratios of observed-to-expected numbers of cases with distance from the transmitter. There was some support for a decline in risk of childhood leukaemia in males, as indicated by Stone's test. The risk also declined for acute myeloid leukaemia in adult females, for all leukaemias (females and all persons separately), and for haematopoietic and lymphatic cancers in females. The same four groups were at higher risks over the whole study area (0–10 km). An increased risk was found for acute lymphatic leukaemia within 2 km of the transmitter; however this was based on only two cases. Elevated risks were found for leukaemias and NHL (males and females combined and separately) over the whole study area. No increase or decrease in the ratios of observed-to-expected numbers of cases was seen for NHL.

Michelozzi *et al.* (2002) published a study on incidence and mortality for adult and childhood leukaemia in an area of 10 km around a high-power radio station in Rome. This station had numerous transmitters with different transmission powers (5–600 kW) operating at different frequencies (short–medium wave). An increased incidence of childhood leukaemia (SIR, 2.2; 95% CI, 1.0–4.1) was found up to 6 km from the radio station; there was a decline with increasing distance from the station for mortality in males and for incidence from childhood leukaemia. [The small number of cases, possible unmeasured confounding and lack of individual or calculated exposure assessment were some limitations of the study.]

Ha *et al.* (2003) published a study on the incidence of cancer in the Republic of Korea in 1993–96 in areas proximate to 42 AM-radio-transmitters, characterized by transmission power. An increased rate ratio comparing sites exposed to high-power versus low-power transmitters was seen for all cancers combined (rate ratio, 1.2; 95% CI, 1.1–1.4), while confidence intervals by cancer type were wide, e.g. for leukaemia (rate ratio, 1.5; 95% CI, 0.7–6.6) and malignant lymphoma (rate ratio, 1.4; 95% CI, 0.6–7.0). However, at two of eleven high-power sites, more pronounced increases in the incidence of leukaemia were found. [Interpretation was hampered by limitations related to the ecological design, study size, exposure and outcome assessment, and lack of controls for confounding. There was partial overlap in the populations included in Park *et al.* (2004) and Ha *et al.* (2007).

Park *et al.* (2004) published a study that evaluated cancer mortality in the Republic of Korea in relation to exposure to AM-radio-transmitters. Mortality from leukaemia was higher in exposed areas than in control areas (standardized mortality rate ratio, MRR, 1.70; 95% CI, 0.84–3.45), particularly among young adults (MRR, 2.44; 95% CI, 1.07–5.24), but also in children (MMR, 2.29; 95% CI, 1.05–5.98). According to the authors, however, there was no increasing or decreasing trend with respect to broadcasting power. [In this study, exposure assessment was poor (no individual data) and it was also unclear to what extent the mortality records reflected the true address of the subject, which was used as a proxy for exposure. Other limitations were the lack of control for confounding by socio-economic status, and possible non-differential disease misclassification.]

(b) Case–control studies

See Table 2.9

Maskarinec *et al.* (1994) published the results of a small case–control study that indicated an increased incidence in childhood leukaemia (SIR, 2.09; 95% CI, 1.08–3.65) near radio towers in Hawaii, USA. The SIR for acute lymphocytic leukaemia was 1.58 (95% CI, 0.63–3.26) and for acute non-lymphocytic leukaemia it was 3.75 (95% CI, 1.20–8.71). Seven cases of leukaemia had been reported during 1982–84, including all five cases of acute non-lymphocytic leukaemia (SIR, 5.34; 95% CI, 2.14–11.0) that were unusual with respect to sex, age, and type of leukaemia. Twelve cases in children aged < 15 years diagnosed with acute leukaemia in 1979–90 and residing in certain census tracts before diagnosis were included in the case–control study, along with 48 (80%) sex- and age-matched controls that lived in the same area at the time of diagnosis. Collection of data was by non-blinded telephone interviews with parents, which included questions on pregnancy, address, and residence history, the child's medical history and exposure of various kinds, including X-rays and smoking. In addition, the occupational history of both parents was recorded, together with potentially relevant exposures. The odds ratio for acute leukaemia among those having lived within 2.6 miles (4.2 km) of the radio towers before diagnosis was increased (OR, 2.0; 95% CI, 0.6–8.3). [The limitations of this study, besides poor assessment of exposure, were its low power to detect an effect (~50% for OR = 5) and the apparent lack of controls for confounding by socioeconomic status.]

Ha *et al.* (2007, 2008) published the results of a case–control study that was large enough to give moderate statistical power for detecting an effect of exposure to RF radiation on the risk of childhood leukaemia. Patients aged < 15 years with leukaemia and controls with respiratory illnesses were selected from 14 hospitals in the Republic of Korea and matched on age, sex and year of diagnosis (1993–99). From a total of 1928 cases of leukaemia and matched controls, risks were estimated by means of conditional logistic regression analysis adjusted for residential area, socioeconomic status and community population density. An increased risk of all types of leukaemia was found among children who lived within 2 km of the nearest AM-radio-transmitter (OR, 2.15; 95% CI, 1.00–4.67). For total exposure to RF radiation, most odds ratios decreased with predicted exposure. The authors reported an odds ratio of 1.40 (95% CI, 1.04–1.88) for lymphocytic leukaemia and 0.63 (95% CI, 0.41–0.97) for myelocytic leukaemia in the quartile of highest peak exposure, although no linear trend was evident with regard to the different exposure categories for total or peak exposure to RF radiation. [The main limitations of the study were related to the exposure estimates calculated by the prediction programme, e.g. the existence of buildings or irregular geographical features was not considered, nor was individual cumulative-exposure history assessed. There was partial overlap in the populations included in Ha *et al.* (2003) and Park *et al.* (2004).]

A case–control study on RF radiation and childhood leukaemia was conducted in west Germany by Merzenich *et al.* (2008). Cases (age, 0–14 years) diagnosed during 1984–2003 and registered at the German Childhood Cancer Registry were included, along with three age-, sex- and transmitter-area-matched controls per case that were drawn randomly from population registries. The analysis included 1959 cases and 5848 controls for which individual exposure to RF radiation 1 year before diagnosis was estimated by means of a field-strength prediction program. The study area encompassed municipalities in the vicinity of Germany's strongest transmitters, including 16 AM and 8 FM transmitters with a power of at least 20 kW. Conditional logistic regression analysis for all types of childhood leukaemia yielded no increase in odds ratio (OR,

Table 2.9 Case–control studies of leukaemia and lymphoma and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comment
Maskarinec *et al.* (1994) Hawaii, USA, 1984–2003	12	48	Hospital	Having lived within 2.6 miles of low-frequency radio towers. Distances estimated both manually and by use of a geographical software package	Acute leukaemia (7 ALL, 5 ANLL)	Last residence before diagnosis within 2.6 miles [4.2 km] of radio towers.	8	2.0 (0.6–8.3)		Matched ORs are given; matching variables: age, sex
						Residence at birth within 2.6 miles of radio towers	8	2.2 (0.3–15)		
						Residence with the maximum number of years within 2.6 miles of radio towers	8	1.8 (0.5–6.3)		
Ha *et al.* (2007) Republic of Korea, 1993–99	1928	3082	Hospital	Prediction program incorporating a geographic information system	All leukaemia (204–208)	*Distance (km)*			Residential location, population density, SES	Conditional logistic regression; matching variables: age, sex, year of diagnosis. Cases aged < 15 yr. Corrected estimates for total RF exposure according to Ha *et al.* (2008)
						> 20	772	1.00		
						≤ 2	36	2.15 (1.00–4.67)		
						> 2–4	73	0.66 (0.44–0.99)		
						> 4–6	120	1.07 (0.77–1.49)		
						> 6–8	218	1.26 (0.96–1.65)		
						> 8–10	276	1.10 (0.85–1.41)		
						> 10–20	428	0.80 (0.65–0.99)		
						Unknown	5	0.48 (0.12–1.95)		
						P for trend		0.10		

Table 2.9 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comment
Ha *et al.* (2007) (contd.)						*Total exposure to RF (mV/m), quartiles (Q)*				In category Q4: OR for LL was 1.40 (95% CI, 1.04–1.88), and for ML, 0.63 (95% CI, 0.41–0.97)
						Q1	737	1.00		
						Q2	362	0.75 (0.58–0.97)		
						Q3	330	0.70 (0.55–0.90)		
						Q4	494	0.83 (0.63–1.08)		
						Unknown	5	0.39 (0.10–1.54)		
						P for trend		0.44		
Merzenich *et al.* (2008) Germany, 1984–2003	1959	5848	Population	Field-strength prediction programme	ICCC Ia, ICCC Ib, ICCC Ic, ICCC Id, ICCC Ie	*Quantiles of median exposure (V/m) to RF-EMFs (AM and FM/TV transmitter) one yr before diagnosis of case*				Conditional logistic regression; matching variables age, sex, year of diagnosis, study region. Cases were aged 0–14 yr.
						0 to < 90%	1772	1.00		
						90 to < 95%	101	1.02 (0.80–1.31)		
						95 to ≤ 100%	86	0.86 (0.67–1.11)		
						Distance (km), AM or FM/TV transmitter				
						10 to < 15	551	1.00		
						0 to < 2	25	1.04 (0.65–1.67)		
						2 to < 6	172	0.81 (0.66–0.99)		
						6 to < 10	314	0.79 (0.67–0.93)		
						≥ 15	866	1.00 (0.88–1.14)		

Table 2.9 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comment
Elliott *et al.* (2010) United Kingdom, 1999–2001	527	5588	Population	(a) Distance from nearest mobile phone base station; (b) Total power output from summation across all base stations within 700 m; (c) Modelled power density at each birth address for base stations within 1400 m	Leukaemia and NHL (C91–95, C82–85)	*Distance from nearest base station (m)*			Percentage of population with education to degree level or higher, Carstairs deprivation score, population density, population mixing	Conditional logistic regression; matching variables: age, sex. Cases aged 0–4 yr
						Lowest	182	1.00		
						Intermediate	167	0.99 (0.78–1.27)		
						Highest	178	1.05 (0.81–1.35)		
						P for trend		0.75		
						Total power output (kW)				
						Lowest	305	1.00		
						Intermediate	112	1.08 (0.84–1.38)		
						Highest	110	1.08 (0.80–1.42)		
						P for trend		0.58		
						Modelled power density (dBm)				
						Lowest	179	1.00		
						Intermediate	179	1.16 (0.90–1.48)		
						Highest	169	1.03 (0.79–1.34)		
						P for trend		0.51		

ALL, acute lymphocytic leukaemia; AM, amplitude modulation; ANLL, acute non-lymphocytic leukaemia; dBm, modelled power density; FM, frequency modulation; ICCC, International Classification of Childhood Cancer; kW, kilowatt; LL, lymphocytic leukaemia; ML, myelocytic leukaemia; OR, odds ratio; NHL, non-Hodgkin lymphoma; RF, radiofrequency radiation; SES, socioeconomic status; TV, television

0.86; 95% CI, 0.67–1.11) when the upper and lower quantiles of RF-radiation distribution were compared. In addition, there was no evidence for an association indicating increased or decreased risk by transmitter type or leukaemia subtype. Nor was there any increased risk (OR, 1.04; 95% CI, 0.65–1.67) for children residing within 2 km of the nearest transmitter. [Lack of information on peak and indoor exposure to RF radiation as well as cumulative lifetime exposure to RF radiation from transmitters, and the low number of cases residing within 2 km of the nearest AM transmitters were the main limitations of this study.]

A case–control study by Elliott *et al.* (2010) (described in Section 2.2.1) examined risk of childhood cancers (e.g. leukaemia and NHL) in association with maternal exposure to RF radiation from mobile-phone base stations during pregnancy. No association or trend for different exposure categories was found for leukaemia or NHL with any of the exposure metrics used. Sociodemographic measures as well as mean distance of birth address from nearest FM, television, and very high frequency (VHF) broadcast antennae were similar for cases and controls. [Although this study had strengths in its size, national coverage and sophisticated exposure assessment compared with previous studies, it was carried out during years when mobile-phone use had become fairly common, yet such usage was not accounted for.]

(c) *Cohort studies*

No data were available to the Working Group.

2.2.3 Other cancers

There have been several small ecological studies, generally of low quality, that have assessed the correlation between all cancers and distance from mobile-phone base stations (Eger *et al.*, 2004; Wolf & Wolf, 2004; Gavin & Catney, 2006; Eger & Neppe, 2009). However, the Working Group considered these studies to be uninformative for the reasons listed below.

Three ecological studies considered risk of all cancers in relation to sources of exposure to RF. Wolf & Wolf (2004) studied the incidence of all cancers around one base station located south of Netanya, Israel, which began operating in July 1996. Among the population of 622 people living within 350 m from the antenna, eight cases were identified between July 1997 and June 1998, and the rate of all cancers among these people was compared to the national rates of cancer in Israel (ratio of rates, 4.15; no confidence intervals provided). [The Working Group considered this study to be uninformative for various reasons, including its small size, unclear method of case ascertainment, crude analyses including incidence rate computed without age standardization, and other methodological limitations.]

Prompted by a reported clustering of cancer cases around a communication mast in Cranlome, Northern Ireland, an ecological study of cancer risk was carried out during 2001–02 (Gavin & Catney, 2006). The mast was erected in 1989, and was taken down in 2002. The Northern Ireland Cancer Registry was the source of case ascertainment. The rates of incidence of groups of cancer in several concentric geographical areas (up to 5 km) were compared with national rates of cancer incidence. The SIR for all cancers was 0.94 (95% CI, 0.88–0.99) for men and 1.00 (95% CI, 0.94–1.06) for women, while the SIR was 101 (95% CI, 79–104) for brain and 99 (95% CI, 74–124) for lymphoma and leukaemia. [The Working Group considered this study to be uninformative due to its small size, the fact that the number of cases was not reported and the absence of evaluation of exposure to RF radiation.]

Eger *et al.* (2004) studied the incidence of all cancers between 1994 and 2003 in areas determined by circles of radius 400 m around two mobile-phone base stations located in Naila, Germany. The first base station became operational in 1993 and the second in 1997. Streets

within and without the area were randomly selected, and the patient databases of general practitioners were searched for cases living the entire period of 10 years at the same address. [The completeness of the ascertainment appeared to be 90%.] The proportion of new cases of cancer was significantly higher among those patients who had lived for the past 10 years at a distance of up to 400 m from the cellular transmitter site, compared with patients living further away. [The Working Group considered this study uninformative due to the small and ill-defined study base and crude statistical methodology.] The same authors investigated the incidence of cancer around a mobile-phone base station in Westphalia, Germany, between 2000 and 2007 (Eger & Neppe, 2009). Twenty-three cases were identified by door-to-door interviews. The authors compared the incidence of all cancers in the 5 years immediately after installation of the mast to that in later years, and found a statistically significant increase in incidence 5 years after the base station started transmission. [The Working Group considered this study to be uninformative due to its small size and crude statistical methodology.]

Five additional studies (Dolk *et al.*, 1997a, b; Ha *et al.*, 2003; Park *et al.*, 2004; Meyer *et al.*, 2006) described information on additional cancer sites (Table 2.10, and see Section 2.2.1). [The interpretation of these results was limited by the small numbers and crude exposure classification.]

2.3 Exposure from mobile phones

With continuing changes in technology, use of mobile phones has become widespread over the last two decades. As a result, the population exposed to RF radiation has greatly increased and is still expanding, with more and more children among its number. Over these two decades, there has been rising concern regarding the potential health risks associated with use of mobile phones, particularly the possibility of increased risk of cancer of the brain. These concerns have stimulated a diverse programme of research, including epidemiological studies carried out to assess the association of mobile-phone use with risk of cancer of the brain and other diseases. The strength of epidemiological studies is obviously the capacity to directly assess the risks associated with use of mobile phones in the general population; however, the observations collected in these studies clearly only address the various exposure scenarios that existed up to the time of observation. Thus the studies carried out to date include few participants who have used mobile phones for > 10–15 years. Any risks that might be associated with lengthier exposure or with a longer interval since first exposure would not be captured by existing studies.

Three types of study design have been applied to address the question whether an increased risk of cancer is associated with RF emitted by mobile phones. These are ecological studies (in particular, observations of time trends in disease rates), case–control studies, and cohort studies. The strengths and limitations of each of these designs in general have been well described. Here, the Working Group focused on the characteristics of these designs as applied to the investigation of the potential risks of mobile-phone use.

Ecological studies provide only indirect evidence on the potential risks associated with mobile-phone use. The general approach involves comparison of time trends in mobile-phone use with time trends in disease indicators, assessing whether the trends are parallel, and allowing for a potential lag in relationships. Over the last few decades, several factors have affected trends in incidence and mortality for cancer of the brain, in particular, the increasing availability of sensitive imaging technology (computed tomography, CT, and magnetic resonance imaging, MRI) for detecting cancers of the brain, which is likely to have had a variable influence on changes in diagnostic practices, depending on country. Consequently, the interpretation of time trends is

Table 2.10 Ecological studies of other cancers and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95%CI)	Covariates	Comments
Dolk *et al.* (1997a) United Kingdom	Around 408 000	1974–86	Distance to Sutton Coldfield radio and TV transmitter	All cancers	Distance 0–2 km Distance 0–10 km Stone's *P* value	703 17 409	1.09 (1.01–1.17) 1.03 (1.02–1.05) Unconditional $P = 0.001$ Conditional $P = 0.462$	Region	
				Skin melanoma	0–2 km	13	1.43 (0.83–2.44)		
				Eye melanoma		0	0 (0–4.22)		
				Male breast		1	1.64 (0.04–9.13)		
				Female breast		107	1.08 (0.90–1.31)		
				Lung		113	1.01 (0.84–1.21)		
				Colorectal		112	1.13 (0.94–1.35)		
				Stomach		33	0.75 (0.54–1.06)		
				Prostate		37	1.13 (0.82–1.55)		
				Bladder		43	1.52 (1.13–2.04)		
				Skin melanoma	0–10 km	189	0.96 (0.83–1.11)	Region	
				Eye melanoma		20	1.16 (0.75–1.80)		
				Male breast		15	0.99 (0.60–1.64)		
				Female breast		2412	1.05 (1.01–1.10)		
				Lung		3466	1.01 (0.98–1.05)		
				Colorectal		2529	1.03 (0.99–1.07)		
				Stomach		1326	1.06 (1.01–1.12)		
				Prostate		785	1.03 (0.96–1.11)		
				Bladder		788	1.08 (1.01–1.16)		
Dolk *et al.* (1997b) United Kingdom	Around 3 390 000	1974–86	Distance to radio and TV transmitters in United Kingdom (excluding Sutton Coldfield)	Skin melanoma	0–2 km	51	1.11 (0.84–1.46)	Region	
				Bladder		209	1.08 (0.94–1.24)		
				Skin melanoma	0–10 km	1540	0.90 (0.85–0.94)		
				Bladder		8307	1.09 (1.06–1.11)		

Table 2.10 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95%CI)	Covariates	Comments
Ha *et al.* (2003) Republic of Korea	From 3 152 to 126 523 persons per area (total not given)	1993–96	kW	Breast cancer	High-power (≥ 100 kW) *vs* low-power (50 kW) transmitter sites	39.7/33.6 per 100 000 person-years	1.2 (0.8–1.7)	Age	
			Transmitter power (kW)	Breast cancer	Sites with transmitter power:				
					100 kW	29	1.29 (0.86–1.86)		
					250 kW	20	0.88 (0.54–1.36)		
					500 kW	41	0.90 (0.64–1.23)		
					1500 kW	3	2.19 (0.45–6.39)		
Park *et al.* (2004) Republic of Korea	8 115 906	1993–95	Regions including AM-radio broadcasting towers of > 100 kW	All cancer	Total exposed *vs* control (unexposed)	6191	1.29 (1.12–1.49)	Age	Direct standardized MRRs are given.
				Oral cavity and pharynx		14	1.21 (0.41–3.57)		
				Oesophagus		49	1.20 (0.71–2.03)		
				Stomach		403	1.18 (0.96–1.44)		
				Colorectum including anus		78	1.33 (0.83–2.11)		
				Liver, including intrahepatic duct		271	1.01 (0.80–1.27)		
				Pancreas		74	1.52 (0.97–2.39)		
				Lung, including trachea		232	1.08 (0.84–1.38)		
				Thyroid		7	1.35 (0.22–8.19)		
				Breast		22	1.38 (0.63–3.02)		
				Bone and connective tissue		8	1.05 (0.21–5.22)		
				Urinary bladder		16	1.13 (0.48–2.65)		
				Skin		8	1.72 (0.36–8.21)		

Table 2.10 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95%CI)	Covariates	Comments
Meyer *et al.* (2006) Germany	177 428 persons living in 48 municipalities in Bavaria		Presence of mobile-telephone relay stations, classified into three categories of relay-station coverage	Breast Brain and CNS Thyroid		NR	NR		Incidence of all cancers combined was not found to be elevated in municipalities with mobile-telephone relay stations. Specific cancers not heterogeneously distributed

AM, amplitude modulation; CNS, central nervous system; kW, kilowatt; MRR, mortality rate ratio; NR, not reported; TV, television

complicated. Nonetheless, the ecological studies provide evidence for consideration in the assessment of the coherence of a causal association of mobile-phone use with cancer of the brain.

The critical evidence comes primarily from case–control studies, as only few cohort studies have been carried out. The basic design of most case–control studies reviewed in this section has involved interviews with cases (most studies are of cancer of the brain) and with appropriate controls; the interviews characterize use of mobile phones, exposures to other sources of RF radiation (e.g. cordless phones) in some instances, potential confounding factors, and other information. The critical methodological concerns around interpretation of the findings of case–control studies of mobile-phone use involve the comparability of cases and controls, the potential for selection bias, and information bias, particularly in ascertainment of exposure to RF radiation from mobile-phone use. Confounding is a less serious concern because, apart from age, the only well-established causal factor for cancer of the brain is ionizing radiation, and also because in the general population the distribution of exposures, primarily from diagnostic irradiation, is unlikely to introduce substantial confounding.

Information bias related to exposure assessment has been a principal concern in interpreting the findings of case–control studies. The investigators have developed interview and questionnaire approaches for ascertaining mobile-phone use and exposure characteristics that attempt to capture the full exposure profile. Key exposure metrics have included the duration of use, call frequency, and cumulative use indicators, the types of device used, and various potential modifiers of exposure, such as use of a hands-free device and the laterality of use. With this approach, some degree of non-differential (random) misclassification of exposure to RF radiation is unavoidable. In studies of the association between protracted exposures and risk of cancer, a related concern is that the key exposure metrics used may not capture the etiologically relevant period of a person's exposure profile (for example, if the effect of a hazard does not persist indefinitely, or appears only after an induction and latency period). Additionally, as in any case–control study, there is the possibility of differential recall according to case status regarding mobile-phone use and other items. Such bias may be in the direction of underreporting, if, for example, cases with tumours of the brain had diminished cognitive function. The bias may be in the direction of over-reporting if, for example, cases were more likely to recall events that might have led to their disease. A validation study carried out with the INTERPHONE Study demonstrated non-differential information bias, as well as the possibility of greater recall of temporally remote use by cases compared with controls (Vrijheid *et al.*, 2009a, b). There is the additional possibility that the degree of measurement error varies from study to study, depending on the interview approach and other factors. While random misclassification generally reduces associations, differential misclassification may increase or decrease observed associations from the "true" underlying association.

Selection bias may also affect the results. Selection bias from two sources is of potential concern: specifically, differential participation by cases and controls that is determined by factors influencing likelihood of exposure. Additional selection bias can arise from the process used to select cases and controls, such that the association is distorted from that in the underlying population. This bias is of particular concern in case–control studies involving cases selected from hospitals or other medical institutions, as the factors that lead to hospitalization and diagnosis may also be associated with the exposure(s) under investigation. Selection bias may reduce or increase the observed association.

In interpreting the results of the case–control studies, consideration was given to the net consequences of selection bias and information

bias to answer the question as to whether the observed association(s) could reflect bias (at least in part), rather than causation. The judgment of the Working Group as to the potential consequences of bias was critical to the classification of the evidence from humans. The complexities in interpretation of the findings of case–control studies of mobile phones and cancer of the brain have been reviewed recently (Ahlbom *et al.*, 2009; Saracci & Samet, 2010).

2.3.1 Cancer of the brain

(a) Ecological studies

Multiple ecological studies have been published that compare time trends in use of mobile phones and incidence and mortality rates of various cancers, primarily brain (Table 2.11). [Because these studies provided only limited and indirect evidence on the risk of cancer potentially associated with mobile-phone use, the Working Group presented a brief synthesis only.] These included two time-trend studies (Lönn *et al.*, 2004; Deltour *et al.*, 2009) in the combined Nordic countries, two in the United Kingdom (Nelson *et al.*, 2006; de Vocht *et al.*, 2011a), three in parts of the USA (Muscat *et al.*, 2006; Propp *et al.*, 2006; Inskip *et al.*, 2010), one each in Japan (Nomura *et al.*, 2011), New Zealand (Cook *et al.*, 2003), Switzerland (Röösli *et al.*, 2007) and Israel (Czerninski *et al.*, 2011), and one in a set of eleven countries (Saika & Katanoda, 2011). Most studies provided some data on the temporal pattern of increasing use of mobile phones, based mostly on annual numbers of private subscriptions and, in a few instances, on estimated prevalence of use. The information on use of mobile phones clearly demonstrated the rapid increase between 1985 and 2000; in some countries, the increase started in about 1990, while in others the increase began later in that decade. In some countries, the reported number of subscriptions had approached the total population of the country in 2000. The number of subscriptions is a surrogate for population exposure to RF radiation, but the number does not reflect temporal changes in patterns of actual usage. Most of these ecological studies had used rates of cancer incidence calculated from data obtained from national or subnational cancer registries, while two studies used mortality rates. In most of these studies, the temporal association between trends in use of mobile phones and cancer incidence was assessed informally and descriptively. [The geographical correlation study carried out in several states of the USA (Lehrer *et al.*, 2011) failed to adequately account for population size and composition.]

Studies that covered a long period between increasing use of mobile phones among the population under investigation and available data on cancer incidence from high-quality cancer registries were most informative for evaluating time trends. In Scandinavia, the rise in use of the mobile phone occurred relatively early. The reported prevalence of mobile-phone use among men aged 40–59 years was 7% in 1989 and reached 28% in 1993 (Deltour *et al.*, 2010). No change in trends in cancer incidence was observed between 1993 and 2003 for this age group, which had the highest proportion of people who started using mobile phones at an early stage (Deltour *et al.*, 2009). In the USA, the use of mobile phones started to increase somewhat later; about 100 million subscribers were registered in 2000, i.e. 36% of the population.(Inskip *et al.*, 2010). According to data collected by the Surveillance, Epidemiology, and End Results (SEER) Program, age- and sex-specific trends and overall temporal trends in rates of incidence of brain cancer in the USA were flat or downward between 1992 and 2006, with the exception of women aged 20–29 years (Inskip *et al.*, 2010). In this age group, a statistically significant increasing trend was driven by the rising incidence in tumours of the frontal lobe. [It is the temporal lobe that is most heavily exposed to radiation when using a mobile phone at the ear (Cardis *et al.*, 2008).]

Table 2.11 Time trends in use of mobile phones and cancer occurrence

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Cook *et al.* (2003)	New Zealand	Proportion of mobile-phone subscribers in the New Zealand population	Sharp increase from 1987 (1%) to 1998 (> 30%), particularly since 1993 (5%)	All brain and salivary gland; temporal lobe; parietal lobe	1986–98	Incidence rates from New Zealand Cancer Registry	Flat trends from 1986 to 1998	No apparent impact of mobile-phone use on incidence of brain cancer. This study could only detect a risk if it occurred within 4 yr of first exposure
Hardell *et al.* (2003)	Sweden	None	Presumably sharp increases between 1980s and 2000	Vestibular schwannoma	1960–98	Incidence rates from Swedish Cancer Registry	Increase from 1960 to 1985, then rather flat	No effect of mobile-phone trends. Too early
Lönn *et al.* (2004)	Denmark, Finland, Norway, Sweden	Proportion of mobile-phone subscribers per year in each country	Sharp increase from 1987 (1–2%) to 1998 (30–50%) particularly after 1993	All brain and subtypes	1969–98	Incidence rates from Nordic National Cancer Registries	Gradual increase from 1968–1983; flat from 1983–96; slight upticks in 1997 and 1998	No apparent impact of mobile-phone use on incidence of brain cancer. Long-standing, high-quality registries. Increased incidence in late 1970s and early 1980s coincides with improvements in diagnosis. This study could only detect a mobile-phone-related risk if it occurred within about 5 yr of first exposure.
Muscat *et al.* (2006)	USA (SEER Program); 17 registries; about one quarter of the USA population	Unclear	From 0% to about 50% of the population; "exponential increase"	Neuronal tumours	1973–2002	Incidence rates from SEER	No change in incidence between two periods (1973–85 and 1986–2002)	No apparent impact of mobile-phone use on incidence of neuronal tumours. No data on year-by-year variability. Not clear when the number of users increased, probably in the early to mid-1990s. Neuronal tumours are extremely rare.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Nelson *et al.* (2006)	England and Wales, United Kingdom	Active mobile-phone subscriptions by year, 1987–2004	Very little before 1993; gradual increase to 1997 (10 million) then sharp annual increase to 2004 (60 million)	Acoustic neuroma	1979–2001	Incidence rates from National Cancer Registry for England and Wales	Gradual increase from 1980 to 1990; sharp increase to 1997; decline to 2000. Rise and decline of acoustic neuroma attributed to changes in diagnosis and registration	No apparent impact of mobile-phone use on incidence of acoustic neuroma. The reason for decline in rates after 1997 is uncertain, but its magnitude illustrates the difficulty of detecting a signal if there is one, against the background noise of statistical variability and methodological challenges. The number of subscriptions, approx. 60 million, is clearly in excess of the number of people with subscriptions in England and Wales.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Propp *et al.* (2006)	Several centres in the USA	None	NR	Acoustic neuroma (vestibular schwannoma)	Los Angeles 1975–98; other centres 1985–99	Incidence rates from the Central Brain Tumor Registry of the USA, and the Los Angeles County Cancer Surveillance Program	Modest, but discernable gradual increases over the period of observation	No apparent impact of mobile-phone use on incidence of acoustic neuroma. Modest increase in risk over the period of time studied (1970s to 1990s) could be due to improvement in diagnosis and registration or to some environmental factor. While the authors present no data on trends in mobile-phone use, it is likely that use increased in the early to mid-1990s. This study could only detect a mobile-phone-related risk if it occurred within about 5 yr of first exposure.
Röösli *et al.* (2007)	Switzerland	Prevalence of mobile phone use by year, with mortality rates	None before 1987; slow increase to 1996 (< 10%) and then sharp increase to 2000 (> 60%)	All brain (ICD-8 code 191)	1969–2002	Mortality rates from Swiss Federal Statistical Office	Gradual increase from 1969 to 2002, reaching a plateau after 1997. Smaller increase in rates after 1987 than before. For the whole period, there was a significant increase for men and women in older age groups, but not in younger ones. From 1987 onwards, rather stable rates in all age groups.	No apparent impact of mobile-phone use on incidence of cancer of the brain. High-quality mortality data. Authors quantify difficulty in detecting risk in such an ecological study. Improvements in survival may influence trends in mortality.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Deltour *et al.* (2009)	Denmark, Finland, Norway, Sweden	Unclear	Use increased from zero in the mid-1980s to 'widespread' in the early 1990s to 'sharply increased' in the mid-1990s.	Glioma and meningioma	1974–2003	Incidence rates from Nordic National Cancer Registries	Very slight increases in incidence from 1974 to 1997; no change after 1998	No apparent impact of mobile-phone use on incidence of cancer of the brain. High-quality registration. Up to 10 yr potential latency
Hardell & Carlberg (2009)	Sweden	None	Presumably sharp increases between 1980s and 2000	Brain, age > 19 yr Acoustic neuroma, age > 19 yr	1970–2007	Incidence rates from Swedish Cancer Registry	Changing annual incidence: 1970–79 (+0.15%) 1980–89 (+1.54%) 1990–99 (–0.25%) 2000–07 (+1.26%) 1970–79 (–1.66%) 1980–89 (+4.86%) 1990–99 (+0.66%) 2000–07 (–7.08%)	No evidence of an impact of mobile-phone use on the risk of acoustic neuroma. No or very weak evidence of an effect of phone use on risk of tumours of the brain. Slightly stronger evidence for increased risk of astrocytoma in the most recent period
Inskip *et al.* (2010)	USA (SEER Program); nine state or regional population-based cancer registries	Number of mobile-phone subscribers in USA by year	From very few in 1990 to 25 million in 1995; 100 million in 2000 and 200 million in 2005	All brain, excluding meningioma and lymphoma	1977–2006	Incidence rates from SEER	Gradual increase in risks from 1977 to 1985; since 1986 the pattern is flat or slightly decreasing. Some age/sex subgroups show increasing trends in some subtypes	No apparent impact of mobile-phone use on incidence of cancer of the brain. Very large numbers of cases. Up to 10 yr of potential latency

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Czerninski *et al.* (2011)	Israel	None	Exposure trend not shown but presumably sharp increase between mid-1980s and 2006	Parotid gland	1970–2006	Incident numbers of cases from Israel National Cancer Registry	Approximate tripling of number of tumours of the parotid gland, with increase starting around 1977 and picking-up around 1990	Authors state that population growth explains part of the increase, but they do not acknowledge the role of ageing of the population. Rates would be more convincing than numbers. While numbers increased greatly after 1998, there were, nevertheless, important increases in numbers of cases before mobile phones could plausibly have caused large numbers of cases.
de Vocht *et al.* (2011a)	England	Mobile-phone subscriptions	Sharp increase from 0 in 1985 to 10 million in 1997 to > 50 million in 2003	All brain and each of 11 subsites	1998–2007	Incidence rates from United Kingdom Office of National Statistics	Linear regression for each of 24 sex/site categories. No significant trend for all cancers combined. Significant increase in incidence of tumours of temporal lobe and decreases in tumours of parietal lobe	No apparent impact of mobile-phone use on incidence of cancer of the brain, except for a small but unconvincing increase in incidence of tumours of the temporal lobe. Up to 10 yr of potential latency. The number of subscriptions, approx. 50 million in 2003, is clearly in excess of the number of people with subscriptions in England.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Nomura *et al.* (2011)	Osaka	None	Presumably sharp increases between 1980s and 2000	Intracranial	1975–2004	Incidence rates from Osaka Cancer Registry	Age 0–1 yr, flat; age 20–74 yr, flat until 1999 then slight decline; age 75 yr, sharp increase to 1983 then flat	No increase in incidence rates in recent years. Increasing rates in early years may have been due to diagnostic improvements.
Saika & Katanoda, (2011)	Study involved 11 countries: Japan, Hong Kong Special Administrative Region, Republic of Korea, USA, Australia, the Russian Federation, United Kingdom, Italy, Spain, France, Germany	None	Presumably sharp increases between 1980s and 2000	Brain and CNS	1990–2005	Mortality rates from WHO database	In most of the 22 country/sex data sets, there was a rather flat or declining rate; only in the Russian Federation and Spain was there an increase among females	No apparent increase in mortality from cancer of the brain. Mortality rates may reflect trends in diagnostic standards and in survival.

NR, not reported; SEER, Surveillance, Epidemiology and End Results; yr, year

In another study, trends in rates of newly diagnosed cases of cancer of the brain in England between 1998 and 2007 were examined (de Vocht *et al.*, 2011a). Overall rates of incidence of cancer of the brain in males or females, or in any specific age group were not increased. However, the incidence of tumours of the temporal lobe increased between 1998 and 2007. In a subsequent letter, the same authors reported separate time trends for the periods 1979–99 and 2000–08. For men, a linear regression of age-adjusted rates showed an overall annual increase in 2000–08 of 3.3% (95% CI, 1.1–5.4), whereas it was 2.0% (95% CI, 1.4–2.6) for 1979–99 (de Vocht *et al.*, 2011b). [The linear regression used for this analysis was not an appropriate method and therefore the 95% confidence intervals reported may not be reliable.] For women, corresponding annual increases were 2.8% (95% CI, 0.9–4.9) for 2000–08 and 1.4% (95% CI, 0.7–2.2) for 1979–99.

[The Working Group noted that time-trend analyses did not provide any indication that the rapid increase in use of mobile phones had been followed by a parallel increase in incidence rates of cancer of the brain. Increases in rates of brain tumours in the 1970s and 1980s had paralleled the introduction and distribution of new diagnostic tools, namely CT and MRI. The Working Group further noted that these descriptive analyses would be null if an excess in cancer risk from mobile-phone use became manifest only decades after phone use began, or if an increase affected only a small proportion of the cases by location.]

(b) Cohort studies

An early attempt to conduct a cohort study in the USA on cancer and mobile-phone use was halted by legal action; consequently, the study did not provide useful results (Dreyer *et al.*, 1999). A retrospective cohort study was conducted in Denmark based on the subscriber lists from the two Danish mobile-phone operating companies, including 420 095 individual (i.e. virtually all non-institutional) subscribers from 1982 to 1995. Using unique identifiers, these subscribers were linked to the Danish Cancer Registry from 1982 onwards. The linkage allowed the identification of all cancers occurring in this cohort, and notably cancers of putative target organs. Expected numbers of cases were based on rates in the Danish population. Two papers appeared, one covering cancer outcomes from 1982 to 1996 (Johansen *et al.*, 2001) and the second covering outcomes from 1982 to 2002 (Schüz *et al.*, 2006c). In the latter, more recent, analysis, the expected rates were computed with cohort members excluded from the reference population by subtracting the number of cases of cancer and person-years observed in the cohort from the corresponding figures for the total Danish population. Approximately 85% of the cohort members were males.

There were various sources of misclassification, as acknowledged by the authors. Members of the reference population, apart from cohort members, may well have used mobile phones, either with subscriptions that were not in their names (e.g. corporate accounts), or with subscriptions taken out after 1995. Moreover, a member of the cohort may have been the official subscriber to an account, but not the true user. Using information from a separate case–control study, it was estimated that as many as 39% of cohort members may not have been mobile-phone users before 1996 and as many as 16% of the reference population may have been users. Using information from Statistics Denmark, it appeared that the cohort members represented a somewhat more affluent section of the Danish population. While the investigators had no data on individual patterns of use, they had information on the year of the individual's first subscription, and this was used to compute SIRs by time since first use. The median duration of subscription among subscribers was 8 years and the maximum was 21 years.

For the entire cohort there was a slight deficit of total cancers among males (SIR, 0.93; 95% CI,

0.92–0.95), and a slight excess among females (SIR, 1.03; 95% CI, 0.99–1.07). For the main cancer types of interest, the results were similarly close to the null value, with relatively narrow confidence intervals, as shown in Table 2.12. For subtypes of cancer of the brain, most SIRs were close to the null value.

The SIR for glioma was 1.01 (95% CI, 0.89–1.14; 257 cases). The odds ratios for glioma in the two lobes closest to the ear showed conflicting results, with a SIR of 1.21 (95% CI, 0.91–1.58) for the temporal lobe and a SIR of 0.58 (95% CI, 0.36–0.89) for the parietal lobe. The SIR was lower for all other areas of the brain, although confidence intervals were overlapping. [Cardis *et al.* (2008) have reported that it is the temporal lobe of the brain that receives the highest percentage of RF radiation deposition (50%).]

The SIR for meningioma was 0.86 (95% CI, 0.67–1.09) and for acoustic neuroma (nerve sheath tumour) it was 0.73 (95% CI, 0.50–1.03). There was no trend in SIR according to years since first subscription, and the subgroup with > 10 years since first subscription had a low SIR for all tumours of the brain and nervous system (SIR, 0.66; 95% CI, 0.44–0.95). [There were few subscribers who began using a mobile phone ≥ 10 years before the end of follow-up. and there was no information on individual levels of mobile-phone use.]

The Danish subscriber cohort study was updated for occurrence of acoustic neuroma (vestibular schwannoma) until 2006 (Schüz *et al.*, 2011). This update and analysis was restricted to a large subset of subscribers and of the Danish population (2.9 million subscribers and non-subscribers) for which independent information was available on each subject's highest level of education, annual disposable income and marital status. Further to the follow-up with data from the Danish cancer registry, a clinical registry of acoustic neuroma was used to achieve completeness of case ascertainment and obtain additional tumour characteristics, such as laterality, and spread and size of the acoustic neuroma. In this cohort analysis, having a long-term mobile-phone subscription of ≥ 11 years was not related to an increased risk of vestibular schwannoma in men (RR, 0.87; 95% CI, 0.52–1.46; adjusted for sociodemographic factors); and no cases of acoustic neuroma occurred among long-term female subscribers versus 1.6 cases expected. Although 53% of Danes reported that they mainly used their phones on the right side, with 35% preferring the left side and 13% having no preferred side, based on data from the launch of a prospective cohort study described in Schüz *et al.*, 2011), acoustic neuroma in the subscriber cohort occurred equally on both sides (48% of tumours were on the right side, with no change in this proportion over time). Acoustic neuromas in long-term male subscribers were not larger than those in non-subscribers and short-term subscribers (mean diameter, 14.6 versus 15.9 mm).

(c) Case–control studies

There have been many case–control studies of tumours of the brain in relation to use of mobile phones: a series from one group in Sweden (this study also included cordless phones), an IARC-coordinated series from 13 countries known as INTERPHONE (this study included use of cordless phones among the unexposed group), and several others, including three from the USA, and one each from Finland, France, Greece and Japan. Some studies considered all major types of tumours of the brain, while others considered glioma and meningioma, or glioma only, or acoustic neuroma only. The studies are presented below by major tumour type. Most studies were based on interviews with study subjects or proxies, and involved questions on history of mobile-phone use. Various exposure metrics were used in the different studies, including binary indicators of ever versus never use, metrics of duration of use, frequency of use, and time since start of use. In addition, some analyses

Table 2.12 Cohort study of cancer of the brain and use of mobile phones

Reference, study location and period	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Comments
Schüz *et al.* (2006c) Denmark,1982–2002	420 095, 357 553 men, 62 542 women	1982–2002	Subscribers to mobile-phone service	All cancers	Ever subscribed	14 291	0.95 (0.93–0.97)	Update of Johansen *et al.* (2001). Median time since first subscription, 8 yr. Expected numbers derived from Danish National Cancer Registry after excluding cohort members from the population. Questionable correspondence between mobile-phone subscriptions and use levels.
					Ever subscribed: men	11 802	0.93 (0.92–0.95)	
					Ever subscribed: women	2 447	1.03 (0.99–1.07)	
				Brain, CNS	Ever subscribed	580	0.97 (NR)	
				Brain, CNS	Ever subscribed: men	491	0.96 (0.87–1.05)	
				Brain, CNS	Ever subscribed: women	89	1.03 (0.82–1.26)	
				Brain, CNS	Latency, < 1 yr since start	51	0.90 (0.67–1.18)	
				Brain, CNS	Latency, 1–4 yr since start	266	1.03 (0.91–1.17)	
				Brain, CNS	Latency, 5–9 yr since start	235	0.96 (0.84–1.09)	
				Brain, CNS	Latency, ≥ 10 yr since start	28	0.66 (0.44–0.95)	
				Glioma (191–191.9)	Ever subscribed	257	1.01 (0.89–1.14)	
				Temporal lobe (191.2)	Ever subscribed	54	1.21 (0.91–1.58)	
				Parietal lobe (191.3)	Ever subscribed	21	0.58 (0.36–0.89)	
				Meningioma (192.1)	Ever subscribed	68	0.86 (0.67–1.09)	
				Nerve sheath tumours (192.0) [a]	Ever subscribed	32	0.73 (0.50–1.03)	

[a] Includes other rare tumours of the nerve sheath

CI, confidence interval; CNS, central nervous system; NR, not reported; yr, year or years

considered modifiers of exposure, such as laterality of mobile-phone use. The latter was based on the premise that if there were a risk related to mobile-phone use, it should manifest itself in a greater proportion of tumours on the side of the head corresponding to the subject's preferred side of phone use. Some studies analysed exposure in relation to the lobe in which the tumour appeared, based on the premise that some lobes absorb more RF radiation than others.

(i) Glioma

See Table 2.13

A case–control study of cancer of the brain was conducted in five academic medical centres in the north-eastern USA during 1994–1998 (Muscat *et al.*, 2000). Interviews were conducted with the cases (n = 469), mainly patients with glioma, and with controls (n = 422) selected from the same medical centres. Analysis of reported histories of mobile-phone use, adjusting for sociodemographic factors, study centre, proxy status, and date of interview, yielded a set of odds-ratio estimates that showed no effect, whether by various exposure metrics, anatomical location of the tumour, or histological subtypes. The only exception was an odds ratio of 2.1 (95% CI, 0.9–4.7) for neuroepitheliomatous tumours (14 exposed cases). [The Working Group noted that the highest prevalence of these tumours occurred in the temporal lobe.] The longest duration of use considered was ≥ 4 years. [The numbers of cases were small, exposure levels were low: of the 422 controls, 346 had never used a mobile phone and 22 had used a mobile phone for ≥ 4 years.]

Inskip *et al.* (2001) conducted a case–control study of tumours of the brain in three centres between 1994 and 1998. A total of 489 cases of glioma were interviewed, as were 799 controls. Compared with non-users, self-reported regular use of mobile phones was not associated with excess risk of glioma (OR, 0.8; 95% CI, 0.6–1.2). Based on very small numbers, there was no indication of excess risk among people with the heaviest (cumulative use, > 500 hours) or longest (5 years or more) use of mobile phones, or any relationship between reported laterality of use and laterality of the tumours, or any relationship with neuroepitheliomatous tumours (OR, 0.5; 95% CI, 0.1–2.0; eight exposed cases). [Of the 799 controls, 625 had never or rarely used a hand-held mobile phone and only 50 had used a hand-held mobile phone before 1993.]

In a case–control study in Finland, the researchers enrolled cases of tumours of the brain and salivary gland occurring in 1996, as well as a 5 : 1 control series selected from the general population (Auvinen *et al.*, 2002). There were 198 cases of glioma. Each subject was linked to a list of all subscribers to the two mobile-phone companies operating in Finland, to establish whether the subject had been a subscriber, for how long, and what type of phone he or she was using (analogue/digital). Linkage of records to the census allowed the investigators to ensure that the case and control series were similar in occupational, socioeconomic and urban/rural characteristics. The odds ratio for glioma was 1.5 (95% CI, 1.0–2.4) for those who had ever had a mobile-phone subscription (about 12% of all subjects), and 1.7 (95% CI, 0.9–3.5) for those who had had a subscription for > 2 years (< 4% of all subjects). When examined separately, the ever-users of analogue phones had an odds ratio for glioma of 2.1 (95% CI, 1.3–3.4) and ever-users of digital phones had an odds ratio of 1.0 (95% CI, 0.5–2.0). [A strength of this study was the linkage of cancer records, population-register records, and mobile-phone subscription records. It was limited by small numbers, inability to assess impact of use of mobile phones for > 2 years, and uncertainty about the correspondence between subscription to a mobile-phone service and individual use of mobile phones.]

Two hospital-based case–control studies (Gousias *et al.*, 2009; Spinelli *et al.*, 2010), one in Greece and the other in France, examined associations between glioma and malignant tumours

of the brain, respectively, and mobile-phone use. The results are summarized in Table 2.13. Neither study was informative due to small numbers and unclear methods of exposure assessment.

The INTERPHONE study, a multicentre case–control study on use of mobile phones and various types of tumour of the brain, is the largest study on this topic so far. The study was coordinated by IARC and conducted in 16 study centres in 13 countries with a common core protocol (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, and the United Kingdom). A detailed description of the study design, epidemiological methods and study population can be found in Cardis *et al.* (2007). In brief, the source population was generally restricted to major metropolitan areas where mobile phones were first introduced and where most of the population was considered to be unlikely to leave the region for diagnosis and treatment. Residents aged between 30 and 59 years were eligible for the study, but somewhat larger age ranges were applied in some of the centres. The study periods also varied somewhat across centres, ranging from 2 to 4 years between 2000 and 2004. Eligible cases were ascertained rapidly through neurological and neurosurgical facilities in the study regions, and completeness of ascertainment was checked with secondary sources (Cardis *et al.*, 2007). Cases had a histologically confirmed or unequivocal imaging-based diagnosis of a first primary glioma, meningioma or acoustic neurinoma. Three centres also included malignant tumours of the parotid gland, and Japan additionally included pituitary tumours. Population controls were randomly selected from population registries (part of Canada, Denmark, Finland, Germany, Italy, Norway, Sweden), electoral lists (Australia, part of Canada, France, New Zealand), patient lists from general practice (United Kingdom) or by random-digit dialling (part of Canada, France, Japan). Controls were individually (part of Canada, France, Japan, New Zealand, United Kingdom) or frequency-matched (remaining countries) to cases on year of birth (within categories of 5 years), sex and study region. One control was recruited for each patient with a tumour of the brain, two for each patient with acoustic neuroma, and three for each patient with a tumour of the parotid gland.

All consenting subjects were interviewed face-to-face by trained interviewers by use of a computer-assisted personal interview (CAPI) whenever possible. If participants had died or were too ill to be interviewed, a proxy was interviewed. The questionnaire covered demographic factors, potential confounders and risk factors for the diseases of interest, including detailed questions on use of mobile phones and other wireless-communication devices. A regular mobile-phone user was defined as having used a mobile phone for at least one call per week during 6 months or more.

Since the first publications of national results in 2004 (Christensen *et al.*, 2004; Lönn *et al.*, 2004), numerous papers have presented results from single countries (Christensen *et al.*, 2005; Lönn *et al.*, 2005; Schoemaker *et al.*, 2005; Hepworth *et al.*, 2006; Schüz *et al.*, 2006a, b; Takebayashi *et al.*, 2006, 2008; Hours *et al.*, 2007; Klaeboe *et al.*, 2007; Schlehofer *et al.*, 2007; Sadetzki *et al.*, 2008; Hartikka *et al.*, 2009) or pooled results from a subset of the INTERPHONE countries, such as the five north European countries: Denmark, Finland, Norway, Sweden, and the United Kingdom (Schoemaker *et al.*, 2005; Lahkola *et al.*, 2007, 2008). In addition, various papers have addressed methodological issues such as exposure misclassification and selection bias (Samkange-Zeeb *et al.*, 2004; Berg *et al.*, 2005; Lahkola *et al.*, 2005; Vrijheid *et al.*, 2006a, b, 2009a, b). The results presented here focus on the pooled results from all countries.

The INTERPHONE Study Group (2010) published the pooled analysis of the INTERPHONE study on the risk of glioma and meningioma in relation to use of mobile phones,

Table 2.13 Case–control studies of glioma and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (1999) Sweden, 1994–96	136	Two controls per case	Population	Self-administered standardized questionnaire	48 glioblastoma, 46 astrocytoma, 19 oliodendroglioma, 3 ependymoma, 16 mixed glioma, and 4 other malignant tumours	Never use of mobile phone Ever use	 53	1.0 1.0 (0.6–1.5)	Age, sex, SEI, and year of diagnosis	
Muscat *et al.* (2000) USA, 1994–98	469	422	In-patients from five USA academic medical centres. Controls from the same hospitals as cases, from daily admission rosters	In-person interviews, history of mobile-phone use	Brain cancer (191.0–191.9)	Ever use Cumulative use (h): 0 > 0 to ≤ 8.7 > 8.7 to ≤ 60 > 60 to ≤ 480 > 480	NR 17 12 19 14	0.7 (0.5–1.1) 1.0 1.0 (0.5–2.0) 0.6 (0.3–1.3) 0.9 (0.5–1.8) 0.7 (0.3–1.4)	Age, education, sex, race, study centre, proxy, year of interview	Analyses showed no associations by year of use. Few subjects with long-term heavy exposure. Response rates were 82% for cases and 90% for controls.
	108	422			Temporal lobe	Ever use	108	0.9 (0.5–1.7)		
	60	422			Parietal lobe	Ever use	60	0.8 (0.3–2.0)		
	354	422			Astrocytic	Ever use	41	0.8 (0.5–1.2)		
	35	422			Neuro-epitheliomatous	Ever use	14	2.1 (0.9–4.7)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Inskip *et al.* (2001) USA, 1994–98	489	799	Patients admitted to the same hospitals for a variety of non-malignant conditions.	Computer-assisted, personal interview in the hospital	Glioma	Cumulative use (h):			Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	There are results for other exposure metrics: average daily use, duration of use, year in which use began. Also results for acoustic neuroma, and for laterality by tumour type.
						Never or rarely used	398	1.0		
						< 13	26	0.8 (0.4–1.4)		
						13–100	26	0.7 (0.4–1.3)		
						> 100	32	0.9 (0.5–1.6)		
						> 500	11	0.5 (0.2–1.3)		
						Regular use	85	0.8 (0.6–1.2)		
						Start of use before 1993	23	0.6 (0.3–1.4)		
Auvinen *et al.* (2002) Finland, 1996	398 (198 glioma)	1990	Population Registry Centre of Finland	Information on subscriptions obtained from the two mobile-network providers operating in Finland in 1996	Glioma (191)	*Analogue*:			Age, sex	Cases, age 20–69 yr
						Ever	26	2.1 (1.3–3.4)		
						< 1 yr	4	1.6 (0.5–5.1)		
						1–2 yr	11	2.4 (1.2–5.1)		
						> 2 yr	11	2.0 (1.0–4.1)		
						Digital:				
						Ever	10	1.0 (0.5–2.0)		
						< 1 yr	3	0.8 (0.2–2.6)		
						1–2 yr	7	1.4 (0.6–3.4)		
						> 2 yr	0	0		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2002b) Sweden, 1997–2000	588	581	Population	Self-administered standardized questionnaire	415 astrocytomas, 6 medullo-blastomas, 54 oligodendro-gliomas, 11 ependymomas, 65 other/mixed gliomas, and 37 other malignant tumours of the brain	Never use of mobile/ cordless phone		1.0 (reference)	Age, sex, SEI, and year of diagnosis	Ipsilateral use of analogue phone was associated with risk of malignant tumour of the brain (OR, 1.8; 95% CI, 1.2–3.0). Ipsilateral use of digital phone was also associated with risk of malignant tumour of the brain (OR, 1.6; 95% CI, 1.1–2.4).
						Analogue, ever use	79	1.1 (0.8–1.6)		
						Digital, ever use	112	1.1 (0.8–1.5)		
						Digital, > 1–6 yr latency	100	1.1 (0.8–1.4)		
						Digital, > 6 yr latency	12	1.7 (0.7–4.3)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2006a,c) Sweden, 2000–03	317	1990	Population	Self-administered standardized questionnaire	248 astrocytomas, and 69 other malignant tumours of the brain	Never use of mobile/ cordless phone	63	1.0	Age, sex, SEI, and year of diagnosis	
						Ever use, analogue	68	2.6 (1.5–4.3)		Analogue phone: Ipsilateral use: 3.1 (95% CI, 1.6–6.2); contralateral use: 2.6 (95% CI, 1.3–5.4)
						Ever use, digital	198	1.9 (1.3–2.7)		Digital phone: Ipsilateral use: 2.6 (95% CI, 1.6–4.1); contralateral use: 1.3 (95% CI, 0.8–2.2)
						Time since start of use, analogue (yr)				
						> 1–5	0	–		
						> 5–10	20	1.8 (0.9–3.5)		
						> 10	48	3.5 (2.0–6.4)		
						Time since start of use, digital (yr)				
						> 1–5	100	1.6 (1.1–2.4)		
						> 5–10	79	2.2 (1.4–3.4)		
						> 10	19	3.6 (1.7–7.5)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2006b) Sweden, 1997–2003	905	2162	Population	Self-administered standardized questionnaire	539 high-grade astrocytomas, 124 low-grade astrocytomas, 93 oligodendrogliomas, 78 other/mixed gliomas and 71 other malignant tumours of the brain	Never use of mobile/cordless phone		1.0 (reference)	Sex, age, SEI, and year of diagnosis	Pooled analysis of case–control data for living cases ascertained from 1997–2000 and 2000–03. See also further results of analyses of these data in Hardell *et al.* (2009)
						Ever use, analogue	178	1.5 (1.1–1.9)		
						Ever use, digital	402	1.3 (1.1–1.6)		
						Time since start of use, analogue (yr)				
						> 1–5	39	1.2 (0.8–1.8)		
						> 5–10	57	1.1 (0.8–1.6)		
						> 10	82	2.4 (1.6–3.4)		
						Time since start of use, digital (yr)				
						> 1–5	265	1.2 (1.0–1.5)		
						> 5–10	118	1.7 (1.2–2.2)		
						> 10	19	2.8 (1.4–5.7)		
						Cumulative call time, analogue (h)				
						1–1000	147	1.3 (1.0–1.7)		
						1000–2000	10	3.0 (1.1–7.7)		
						> 2000	21	5.9 (2.5–14)		
						Cumulative call time, digital (h)				
						1–1000	355	1.3 (1.0–1.6)		
						1001–2000	26	1.8 (1.0–3.1)		
						> 2000	21	3.7 (1.7–7.7)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2006b) (cont.)						*Ipsilateral use, analogue:*				
					All malignant		95	2.1 (1.5–2.9)		
					High-grade astrocytoma		62	2.4 (1.6–3.6)		
					Low-grade astrocytoma		10	1.8 (0.8–4.1)		
						Contralateral use, analogue:				
					All malignant		54	1.1 (0.8–1.6)		
					High-grade astrocytoma		37	1.6 (1.0–2.5)		
					Low-grade astrocytoma		4	0.5 (0.2–1.6)		
						Ipsilateral use, digital:				
					All malignant		195	1.8 (1.4–2.4)		
					High-grade astrocytoma		127	2.3 (1.7–3.1)		
					Low-grade astrocytoma		27	1.9 (1.0–3.5)		
						Contralateral use, digital:				
					All malignant		119	1.0 (0.7–1.3)		
					High-grade astrocytoma		69	1.1 (0.8–1.5)		
					Low-grade astrocytoma		16	1.1 (0.5–2.1)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Gousias *et al.* (2009) Greece, 2005–07	41	82	Neuro-surgery patients	In-person interviews, history of mobile phone use	Glioma	Minutes per year of mobile-phone use	NR	1.00 (0.99–1.01)	Age, sex, residence area, smoking, alcohol, head trauma	Not informative because of low power and too finely resolved exposure metric
Hardell *et al.* (2010) Sweden, 1997–2003	346	343 cancer controls, 276 other controls	Swedish Death Registry	Interviews with relative of decedent	314 gliomas and 32 other malignant tumours of the brain	Never use of mobile/ cordless phone		1.0	Sex, age, SEI, and year of diagnosis	Analysis of deceased cases (and controls) only
						Ever use, analogue	61	1.7 (1.1–2.7)		
						Ever use, digital	83	1.4 (1.0–2.1)		
						Cumulative call time, analogue (h)				
						1–1000	41	1.5 (1.0–2.5)		
						1001–2000	5	1.1 (0.3–3.3)		
						> 2000	15	5.1 (1.8–14)		
						Cumulative call time, digital (h)				
						1–1000	58	1.2 (0.8–1.8)		
						1001–2000	8	2.6 (0.9–8.0)		
						> 2000	17	3.4 (1.5–8.1)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Spinelli *et al.* (2010) France, 2005	122	122	In-patients from neurosurgery departments of the same hospitals; unrelated to cancer	In-person interviews	Malignant primary tumours of the brain, 72 glioblastomas	Subscription hours/year			Sex, age	Unclear criteria for recruitment; small numbers
						0	37	1.0		
						< 4	8	0.9 (0.3–2.4)		
						4–36	58	1.4 (0.8–2.8)		
						≥ 36	13	1.1 (0.4–2.8)		
INTERPHONE Study Group (2010) Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, United Kingdom, 2000–04	2708	2972	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Glioma (D33.0, D43.0–43.9, C71.0–71.9)	Never regular use of mobile phone	1042	1.0 (ref.)	Sex, age, study centre, ethnicity (in Israel) and education	OR highest in short-term users (start of mobile phone use, 1–4 yr before reference date) (OR, 3.77; 95% CI, 1.25–11.4, based on eight cases)
						Regular use	1666	0.81 (0.70–0.94)		
						Time since start of use (yr)				
						1.5	156	0.62 (0.46–0.81)		
						2–4	644	0.84 (0.70–1.00)		
						5–9	614	0.81 (0.60–0.97)		
						≥ 10	252	0.98 (0.76–1.26)		
						Cumulative call time with no hands-free devices (h)				
						< 5	141	0.70 (0.52–0.94)		
						5–12.9	145	0.71 (0.53–0.94)		
						13–30.9	189	1.05 (0.79–1.38)		
						31–60.9	144	0.74 (0.55–0.98)		
						61–114.9	171	0.81 (0.61–1.08)		
						115–199.9	160	0.73 (0.54–0.98)		
						200–359.9	158	0.76 (0.57–1.01)		
						360–734.9	189	0.82 (0.62–1.08)		
						735–1639.9	159	0.71 (0.53–0.96)		
						≥ 1 640	210	1.40 (1.03–1.89)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2011a) Sweden, 1997–2003	1148	2438	Population	Self-administered standardized questionnaire	Glioma	Never use of mobile/cordless phone		1.0	Sex, age, SEI, and year of diagnosis	Pooled analysis of case–control data for living cases ascertained from 1997–2000, and 2000–03, as well as case–control data for deceased cases 1997–2003.
						Ever use (mobile phone)	529	1.3 (1.1–1.6)		
						Time since start of use (yr)				
						> 1–5	250	1.1 (0.9–1.4)		
						> 5–10	156	1.3 (1.0–1.6)		
						> 10	123	2.5 (1.8–3.3)		
						Cumulative call time, mobile phone (h)				
						1–1000	427	1.2 (1.03–1.5)		
						1001–2000	44	1.8 (1.2–2.8)		
						> 2000	58	3.2 (2.0–5.1)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Cardis *et al.* (2011) Australia, Canada, France, Israel, Italy, New Zealand, 2000–04	553	1762	Population	Interviewer-administered standardized questionnaire	Glioma (D33.0, D43.0–43.9, C71.0–71.9)	*RF TCSE (J/kg)*			Sex, age, study centre, ethnicity (in Israel) and education	Interpretation of OR is most meaningful when compared with the corresponding OR for comparable exposure surrogates of mobile-phone use. When stratified for different time windows of time before diagnosis, the OR tended to increase with increasing TSCE for use ≥ 7 yr in the past. For the highest exposure quintile: OR, 1.91 (95% CI, 1.05–3.47)
						< 76.7	67	0.76 (0.53–1.09)		
						76.7–	68	0.94 (0.66–1.35)		
						284.1–	60	0.80 (0.54–1.18)		
						978.9–	57	0.89 (0.61–1.30)		
						3123.9+	103	1.35 (0.96–1.90)		
						Case-only analyses:				
						Ever regular user	30	1.35 (0.64–2.87)		
						Time since start of use (yr)				
						1–4	12	1.37 (0.59–3.19)		
						5–9	7	0.72 (0.27–1.90)		
						≥ 10	11	2.80 (1.13–6.94)		
						Cumulative call time without hands-free devices (h)				
						< 39	6	1.19 (0.40–3.51)		
						39–220	4	0.93 (0.27–3.14)		
						220–520	5	1.38 (0.42–4.53)		
						520–1147	10	2.55 (0.94–6.91)		
						> 1147	5	0.99 (0.30–3.27)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Larjavaara *et al.* (2011) Denmark, Finland, Germany, Italy, Norway, Sweden, south-eastern England, 2000–04	888		Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Glioma (D33.0, D43.0–43.9, C71.0–71.9)	Never-regular use of mobile phone	91		Country, sex, age group, and SES	Case–case analysis
						Regular use	107	0.80 (0.56–1.15)		ORs are for a distance of ≤ 5 cm between the glioma midpoint and the typical source of mobile-phone exposure in regular mobile-phone users, compared with never-regular users
						Duration of use (yr)				
						1.5–4	65	0.85 (0.57–1.25)		
						5–9	30	0.71 (0.43–1.18)		
						≥ 10	10	0.85 (0.39–1.86)		
						Cumulative call time (h)				
						0.001–46	33	0.82 (0.51–1.31)		
						47–339	38	0.97 (0.60–1.56)		
						> 339	30	0.58 (0.35–0.96)		
						Laterality of use				
						Ipsilateral	51	0.80 (0.52–1.22)		
						Contralateral	37	0.77 (0.47–1.24)		
						Never regular use of mobile phone	91	1.30 (0.95–1.80)	Within-subject comparison	Case–specular analysis
						Regular use	107	1.19 (0.89–1.59)		
						Duration of use (yr)				
						1.5–4	65	1.15 (0.80–1.66)		
						5–9	30	1.04 (0.61–1.76)		
						≥ 10	10	2.00 (0.68–5.85)		
						Cumulative call time (h)				
						0.001–46	33	1.39 (0.81–2.38)		
						47–339	38	1.21 (0.74–1.97)		
						> 339	30	1.00 (0.59–1.69)		

GP, general practitioner; h, hour; NR, not reported; OR, odds ratio; RF, radiofrequency radiation; SEI, socioeconomic index; SES, socioeconomic status; TCSE, total cumulative specific energy; yr, year

and included 2708 cases of glioma and 2972 controls. The study included 252 cases of glioma and 232 controls who had first used a mobile phone at least 10 years before the reference date. Participation rates were 64% among cases of glioma and 53% among controls. There was wide variation in participation rates for controls between study centres (42–74%).

For regular users, the odds ratio for glioma was 0.81 (95% CI, 0.70–0.94) (Table 2.13). In most study centres, odds ratios of < 1.0 were also seen for all categories of time since start of use and of cumulative number of calls. [The reason for these low odds ratios was not established. While it is plausible that this may in part reflect selection/participation biases, sensitivity analyses carried out by Vrijheid *et al.* (2009a) indicated that it was unlikely to fully explain these results.] In terms of cumulative call time, all odds ratios were < 1.0 for all deciles of exposure except the highest (10th) decile (> 1640 hours). For this exposure group, the odds ratio for glioma was 1.40 (95% CI, 1.03–1.89). There were 252 cases and 253 controls who reported start of use ≥ 10 years before the reference date. The odds ratio for the highest exposure decile of cumulative call time dropped from 1.40 to 1.27 when subjects (both controls and cases) who reported use > 5 hours per day were excluded from the analysis. When mobile-phone use was truncated at 5 hours, the odds ratio was 1.38 (95% CI, 1.02–1.87). [There was reasonable doubt about the credibility of such reports and it is possible that the excess of cases in those with unreasonably high values reflected a general tendency for cases to overestimate more than controls, which could contribute to the apparent excess risk in the highest decile. As noted earlier, there is evidence that cases tended to overestimate their past exposure more than controls (Vrijheid *et al.*, 2009a).] For cases of glioma, the proportion of proxy respondents, the number of imputations for missing values, and the proportion of subjects judged by their interviewer to be non-responsive or having poor memory were all higher than for controls (INTERPHONE Study Group, 2010). However, sensitivity analyses showed that these differences by themselves did not explain the results seen in the highest decile of cumulative call time. More information on the various methodological issues and corresponding sensitivity analyses were discussed by the INTERPHONE Study Group (2010)] There was no evidence of heterogeneity in effect across study centres.

More detailed analyses were conducted by the INTERPHONE study team to evaluate the possible association between mobile-phone use and risk of glioma. The odds ratio in the highest exposure decile of cumulative use was larger for tumours in the highly exposed temporal lobe (OR, 1.87; 95% CI, 1.09–3.22) than in the less exposed parietal or frontal lobes (OR, 1.25; 95% CI, 0.81–1.91) or for tumours in other locations (OR, 0.91; 95% CI, 0.33–2.51). This result was consistent with patterns of energy deposition in the brain (Cardis *et al.*, 2008).

The ratio of the odds ratios for ipsilateral phone use to those for contralateral use increased steadily with increasing cumulative number of calls. [This would be expected if there were an exposure–response association.] However, notwithstanding similar trends in higher exposure categories, the highest ratios of these odds ratios for cumulative call time and for time since start of use were observed in the lowest exposure categories. [While these odds ratios were highly imprecise, this pattern may suggest bias in recall of side of phone use.]

In Appendix 2 of the INTERPHONE Study Group (2010) publication, an additional analysis was reported in which never-regular users were excluded from the analysis and the lowest exposure category was used as the reference category. This analysis was based on the assumption that participation bias was the principal explanation for the decreased odds ratios of the main analysis and that bias was related only to mobile-phone user status and not to extent of use. As a result,

most of the odds ratios for glioma increased above unity. Increased odds ratios were found for people who started to use their phone 2–4 years before diagnosis (OR, 1.7; 95% CI, 1.2–2.4), 5–9 years before diagnosis (OR, 1.5; 95% CI, 1.1–2.2) or > 10 years before diagnosis (OR, 2.2; 95% CI, 1.4–3.3). In terms of cumulative call time, the odds ratio for glioma did not show an upward trend for the first nine deciles of exposure, but the odds ratio for the highest category (> 1640 hours) was increased (OR, 1.8; 95% CI, 1.2–2.9).

Some publications of the results for glioma from national INTERPHONE centres were based on broader eligibility criteria, e.g. extending the age range to 20–70 years (Christensen *et al.*, 2005). Inclusion of additional cases did not yield markedly different results in these national publications compared with the pooled analysis.

[The strengths of the INTERPHONE study included its large sample size, the common core protocol, comprehensive data collection and in-depth data analyses (including a wide variety of sensitivity and validation analyses), and its use of population-based controls. The exposure assessment was, however, a limitation. As in most other case–control studies, mobile-phone use was estimated from retrospectively collected interview data and thus recall error was an issue. According to a comparison of self-reported mobile-phone use with operator-recorded data in a comparatively small sample of INTERPHONE participants from Australia, Canada and Italy, little differential exposure misclassification between cases and controls was found on average. However, in the highest category of cumulative number of calls, overestimation was more pronounced in cases than in controls (Vrijheid *et al.*, 2009a). Furthermore, the ratio of self-reported phone use to recorded phone use increased with increasing time before the interview to a greater degree in cases than in controls. Such a pattern could explain an increased risk in the most extreme exposure categories. However, the number of subjects with long-term data was relatively small and recall could only be assessed for 4–6 years at most.

Another limitation of the INTERPHONE study was the relatively low participation rate, particularly for controls (53%), which was less than that for cases (patients with glioma, 64%; meningioma, 78%; acoustic neuroma, 82%). This offered the potential for differentially selective study participation; and there is evidence that people who had ever used mobile phones regularly were more likely to agree to participate than people who had never used mobile phones regularly (Lahkola *et al.*, 2005; Vrijheid *et al.*, 2009b). This would produce downwardly biased estimates of relative risk. [The Working Group noted that a strength of this study was its use of population-based controls and the relatively high participation rate of cases.]

In summary, there was no increased risk of glioma associated with having ever been a regular user of mobile phones in the INTERPHONE study. There were suggestions of an increased risk of glioma in the group in the highest decile of exposure, for ipsilateral exposures, and for tumours of the temporal lobe [although chance, bias or confounding may explain this increased risk].

After publication of the pooled data on glioma, additional analyses were undertaken by the INTERPHONE researchers to evaluate the association between mobile-phone use and risk of glioma. They included refined dose estimation, case–case analyses, and case–specular analyses. Each of these analyses has its merits in complementing the overall picture and in evaluating the role of bias, as discussed below.

Refined dose estimation

In principle, a measure of absorbed RF radiation should be a more biologically relevant metric than "use" of mobile phones, if estimated accurately. In an attempt to derive a more biologically relevant metric, data from five INTERPHONE countries (Australia, Canada, France, Israel and

New Zealand) were used to examine the associations of tumours of the brain with RF fields from mobile phones by estimating the total cumulative specific-energy (TCSE) dose for each individual (Cardis *et al.*, 2011). For each case, the location of the tumour was determined by neuroradiologists and the centre of the tumour was estimated by a computer algorithm (Israel) or by the neuroradiologist (most participants in the other countries). This analogous tumour location was allocated to the controls matched to each case. Matching was done *post hoc* by use of an algorithm that optimized matching on interview time and age within strata defined by sex, region and, in Israel, country of birth. The number of controls per case varied from 1 to 19 (median, 3).

For each study participant, the TCSE was calculated with an algorithm considering the frequency band and communication system of all phones the subject had used, multiplied by call duration. In addition, laterality, use of hands-free devices, network characteristics and urban or rural residence were taken into account (for details, see Cardis *et al.*, 2011). A census of TCSE was carried out 1 year before the reference date.

For the glioma analysis, the 553 cases of glioma for which localization data and communication-systems information were available (42% of all eligible cases) and their 1762 controls (36% of ascertained controls) were included. Odds ratios for glioma were < 1.0 in the first four quintiles of TCSE. In the highest quintile, the odds ratio for glioma was 1.35 (95% CI, 0.96–1.90). Various sensitivity analyses did not markedly affect this odds ratio. Odds ratios in categories of TCSE were also examined in time windows since first use of a mobile phone. There was a fairly consistent dose–response pattern with an odds ratio of 1.91 (95% CI, 1.05–3.47) in the highest exposure quintile when considering TCSE exposure ≥ 7 years before the reference date. There was little evidence of an association for exposures in more recent time windows. [The Working Group noted that TCSE was highly correlated with cumulative call time (weighted kappa, 0.68). As this exposure surrogate was mainly determined by self-reported data, recall and selection bias were of concern, as they were for the other INTERPHONE analyses. Results from TCSE analyses were similar to those for cumulative duration of mobile-phone use.]

Case–case analyses

This is a novel approach for studying the effect of radiofrequency fields emitted by mobile phones. As it is based on cases only, differential participation and recall error between cases and controls is not of concern. In both studies presented below, reported preferred side of use was not considered for determining exposed brain areas. While, this should reduce the possible impact of recall bias, it probably also introduces exposure misclassification, which is expected to be random and thus would bias any risk estimates towards unity.

The same database of five countries discussed above (Cardis *et al.*, 2011) was used to conduct a case–case analysis by comparing the characteristics of mobile-phone use among people with tumours in highly exposed areas of the brain, defined as areas absorbing > 50% of the specific absorption rate (SAR) from use of mobile phones at both sides of the head (i.e. without taking into account laterality), with the corresponding characteristics of people with tumours in other parts of the brain. Comparisons were made with respect to time since first use of a mobile phone and cumulative call time. The odds ratio for presence of the tumour in the most exposed part of the brain for people who had started using a mobile-phone ≥ 10 years previously was 2.80 (95% CI, 1.13–6.94; based on 11 exposed cases), but it was not increased for people who had started using a mobile-phone more recently. There was, in addition, moderate but inconsistent evidence that the odds ratio for presence of a tumour in the most exposed area increased with increasing cumulative call time.

Data from seven INTERPHONE European countries (Denmark, Finland, Germany, Italy, Norway, Sweden, and south-eastern England) were also used to conduct a case–case analysis (Larjavaara *et al.*, 2011). In total, 888 cases of glioma in people aged between 18 and 69 years were included. For each case, the tumour midpoint on a three-dimensional grid was defined, based on radiological images. The distance to the estimated axis of a mobile phone in use on the same side of the head as the glioma was calculated, irrespective of the patient's reported typical side of phone use. Regression models were then computed to compare distance between the midpoint of the glioma and the mobile-phone axis for various exposure groups of self-reported mobile-phone use. In addition, unconditional logistic regression models were applied for the number of tumours occurring at a distance of ≤ 5 cm from the phone axis.

These analyses did not suggest an association between mobile-phone use and distance of glioma from the mobile-phone axis. For instance, the mean distance between tumour midpoint and the phone axis was similar among never-regular mobile-phone users and regular users (6.19 versus 6.29 cm; $P = 0.39$). In the dichotomized analysis examining the occurrence of tumours at a distance of ≤ 5 cm from the phone axis, odds ratios were below unity for the most exposed groups relative to never-regular users. [A limitation of the study was that exposed areas were defined on the basis of distance from the phone axis only; there were no dosimetric calculations. The results of analyses of the spatial distribution of SAR from more than 100 mobile phones (Cardis *et al.*, 2008) showed that, although there was some variability, most exposure occurs in areas of the brain closest to the ear. Exposure is not evenly distributed along the phone axis; thus the approach used could result in substantial misclassification of exposure.]

Case–specular analysis

In the case–specular analysis, a hypothetical control location is defined in the head of each patient with glioma. This was done for the data from the seven European countries described above (Larjavaara *et al.*, 2011) by symmetrically reflecting the location of the actual tumour site across the midpoint of the axial and coronal planes to obtain the mirror-image location as the control location. This counterfactual control site and the location of the actual case site were compared with respect to their distances orthogonal to the mobile-phone axis. An association would be indicated if the odds ratio increased systematically with the amount of exposure; however, this pattern was not observed. The odds ratio was larger for never-regular users than regular users. There was no increasing odds ratio for increasing use of cumulative call time.

[The strength of case–specular analysis is that each subject is his/her own control. Nevertheless, the analysis relies on self-reported use of mobile phones when comparing odds ratio between various strata. Thus exposure misclassification affects the analysis. Never-regular users were, on average, older and more commonly female, and if these factors were to affect the tumour location, bias could be introduced. However, there was little indication for this. A limitation of the study was the small number of long-term users in the case-specular analysis, resulting in wide confidence intervals. As noted above, the absence of dosimetric calculations and use of distance to the phone axis rather than to the most exposed part of the brain was a limitation.]

Hardell *et al.* (1999, 2000, 2001, 2002a, b, 2003, 2006a, b, 2009, 2010, 2011a) have published a series of papers reporting findings regarding associations between use of mobile phones and tumours of the brain. All these epidemiological analyses have been of the case–control design, with cases identified from records of regional cancer registries in Sweden and controls

identified from the Swedish population register or the Swedish death registry (the latter was used when sampling controls for deceased cases). [While reported in a series of publications, the Working Group noted that this research had involved the ongoing collection of case–control data over an extended period of time using a fixed protocol. The Working Group noted that a strength of these analyses followed from the early, and widespread, use of mobile phones in Sweden, implying a population that has accrued exposures from mobile phones over a relatively long time period (analogue phones have been in use since the early 1980s). The fairly long-term exposure from mobile phones permits consideration of any effect that may appear after a more protracted period of exposure than in other locations. Consequently, Hardell *et al.* could address higher cumulative exposures (when measured in terms of total duration of phone use), and include people using devices designed with early mobile-phone technologies, which tended to have higher power output than those based on later mobile-phone technologies.]

In the latest paper available, Hardell *et al.* (2011a) reported the findings of a pooled analysis of associations between mobile- and cordless-phone use and glioma. Cases were ascertained from 1 January 1997 to 30 June 2000 from population-based cancer registries in Uppsala-Orebro, Stockholm, Linkoping, and Gothenburg, and from 1 July 2000 to 31 December 2003 in Uppsala-Orebro and Linkoping. Eligible cases were aged 20–80 years at diagnosis. Population controls were selected from the Swedish population registry, which includes all residents; controls were matched to cases based on calendar year of diagnosis as well as age (within 5-year categories), sex and study region. Deceased controls for deceased cases were selected from the death registry. Environmental and occupational exposures were assessed by a self-administered 20-page questionnaire sent out by post. The questionnaire solicited information regarding demographic characteristics, occupational history, and other potential risk factors for cancer of the brain, and asked detailed questions on use of mobile phones and other wireless communication technologies, including year of first use, type of phone, average number of minutes of daily use, and side of head on which the phone had been used most frequently. A maximum of two reminders was sent if the questionnaire was not completed. A trained interviewer, using a structured protocol, carried out supplementary phone interviews to verify information provided in the questionnaire. Questionnaires were assigned an identification code such that the phone interviews and coding of data from questionnaires were blinded to case–control status. Study participants were asked again as to the side of head on which a phone had been used most frequently. [The Working Group noted that bias could be introduced by such an interview process; Hardell *et al.* (2002a) provided some information regarding classification of cases and controls with respect mobile-phone use based on the questionnaire, and the participants' classification after supplementary interview.] All study participants using mobile or cordless phones were sent an additional letter to re-solicit information on the side of the head on which the phone had been used most frequently. Details regarding the exposure assessment are reported in Hardell *et al.* (2006a, b). For deceased participants, an interview with a proxy (relative of the deceased) was conducted. Exposure was defined as reported use of a mobile phone and separately reported use of a cordless phone; exposure in the year immediately before case diagnosis or control selection was not included.

Cumulative lifetime use in hours was dichotomized by use of the median number of hours among controls as a cut-off point; and, lifetime use in hours was categorized into the following groups: 1–1000, 1001–2000, and ≥ 2000 hours. Three categories of time since exposure were considered > 1–5 years, > 5–10 years, and

> 10 years. Primary statistical analyses were conducted using unconditional and conditional logistic regression models with adjustment for sex, age, socioeconomic index, and year of diagnosis. Participation rates were 85% among cases and 84% among controls.

The analysis included 1148 cases with a histopathological diagnosis of glioma (Hardell *et al.*, 2011a). When mobile-phone users were compared with people who reported no use of mobile or cordless phones, or exposure > 1 year before the reference date, the odds ratio for glioma was reported to be 1.3 (95% CI, 1.1–1.6) (Table 2.13). For study participants who first used a mobile phone ≥ 10 years before the reference date, the odds ratio was 2.5 (95% CI, 1.8–3.3). This study included 123 cases of glioma and 106 controls among those who first used a mobile phone ≥ 10 years before the reference date. In terms of cumulative call time using a mobile phone, odds ratios for glioma increased with increasing categories of lifetime exposure. For the highest exposure group (> 2000 hours), the odds ratio was 3.2 (95% CI, 2.0–5.1). Use of cordless phones was also associated with glioma: the odds ratios for 1–1000 hours, 1001–2000 hours and > 2000 hours of use were 1.2 (95% CI, 0.95–1.4), 2.0 (95% CI, 1.4–3.1), and 2.2 (95% CI, 1.4–3.2), respectively. When considering age at first use, the odds ratio for mobile-phone use for all malignant tumours of the brain was 2.9 (95% CI, 1.3–6.0) for ages < 20 years, 1.3 (95% CI, 1.1–1.6) for ages 20–49 years, and 1.2 (95% CI, 1.0–1.5) for ages ≥ 50 years.

[The Working Group noted that information obtained from next of kin may be less reliable than that from living cases and controls. Analyses reported by Hardell *et al.* that are based solely on information obtained from living cases and controls are not affected by the same concerns about bias arising from information obtained from next of kin.] Excluding deceased cases (and affiliated controls) yielded odds ratios of 1.5 (95% CI, 1.1–1.9) for ever-use of analogue phones, 1.3 (95% CI, 1.1–1.6) for ever-use of digital phones, and 1.3 (95% CI, 1.1–1.6) for ever-use of cordless phones Hardell *et al.* (2006a).

Information on laterality of phone use was collected only from living cases and controls. Pooled case–control analyses were restricted to 905 living cases with malignant tumours of the brain and 2162 controls (Hardell *et al.*, 2006b; Hardell & Carlberg, 2009). Of the cases, 663 were astrocytomas (grades I–IV), 93 were oligodendrogliomas, and the remainder were other malignant tumours of the brain. Participation rates were 90% among cases with malignant tumours and 89% among controls. For users of analogue and digital mobile phones, an increased odds ratio was seen for all malignant tumours of the brain and high-grade astrocytomas with ipsilateral use of mobile phones and with the tumour on the same side of the head, but no increased risk for contralateral use of mobile phones when compared with people who had not used mobile or cordless phones (Table 2.13). [The Working Group noted that a strength of this study was its use of population-based controls and the high participation rate of cases and of controls.]

An earlier report by Hardell *et al.* included a different set of cases of tumours of the brain ascertained during 1994–96 in Uppsala and 1995–96 in Stockholm (Hardell *et al.*, 1999). Participation rates were 90% among cases and 91% among controls. The analyses included 136 cases of malignant tumours of the brain (including 48 cases of glioblastoma, 46 cases of astrocytoma, and 19 cases of oligodendroglioma), with controls matched on sex, age, and region. Of the 425 controls, 161 reported ever having used a mobile phone and 85 reported having used a mobile phone for > 136 hours. Use of a mobile phone was not associated with an increased risk of malignant tumours of the brain (OR, 1.0; 95% CI, 0.7–1.4). [The Working Group noted that a strength of the study was the high participation rates of cases and controls.]

It is useful to consider variation in effect estimates by calendar period. Among cases ascertained during 1997–2000 there were 588 malignant tumours of the brain, including 415 cases of astrocytoma and 54 cases of oligodendroglioma. Ever-use of analogue phones yielded an odds ratio of 1.13 (95% CI, 0.82–1.57), with the odds ratio for ipsilateral use being 1.85 (95% CI, 1.16–2.96) and the odds ratio for contralateral use being 0.62 (95% CI, 0.35–1.11). Ever-use of digital phones yielded an odds ratio of 1.13 (95% CI, 0.86–1.48), with an odds ratio for ipsilateral use of 1.59 (95% CI, 1.05–2.41) and an odds ratio for contralateral use of 0.86 (95% CI, 0.53–1.39) (Hardell *et al.*, 2002b).

Among cases ascertained in 2000–2003, there were 359 malignant tumours of the brain, including 248 cases of astrocytoma and 69 other malignant tumours. Ever-use of analogue phones yielded an odds ratio of 2.6 (95% CI, 1.5–4.3), with 3.1 (95% CI, 1.6–6.2) for ipsilateral use and 2.6 (95% CI,1.3–5.4) for contralateral use; and, ever-use of digital phones yielded an odds ratio of 1.9 (95% CI, 1.3–2.7) with 2.6 (95% CI, 1.6–4.1) for ipsilateral use and 1.3 (95% CI, 0.8–2.2) for contralateral use. Estimates of an association tended to be larger for use beginning > 10 years before diagnosis (Hardell *et al.*, 2006c).

(ii) Meningioma

See Table 2.14

In the case–control study of Inskip *et al.* (2001) mentioned above, interviews were conducted with a total of 197 cases of meningioma and 799 controls. Compared with non-users, self-reported regular users of mobile phones did not manifest excess risks of meningioma (OR, 0.8; 95% CI, 0.4–1.3).

The Finnish case–control study mentioned above (Auvinen *et al.*, 2002) included 129 cases of meningioma. The odds ratio for ever-use was 1.1 (95% CI, 0.5–2.4), with a slightly higher odds ratio for use of analogue phones (OR, 1.5; 95% CI, 0.6–3.5). [This study was limited by the short time since first use of a mobile phone for most people and by the uncertain mobile-phone use ascertainment from subscription information.]

In the pooled INTERPHONE analysis, 2409 cases of meningioma and 2662 controls were included (INTERPHONE Study Group, 2010). Participation rates were 78% for cases of meningioma and 53% for controls. For regular users, a reduced odds ratio was seen for cases of meningioma (OR, 0.79; 95% CI, 0.68–0.91) (see Table 2.14). Odds ratios of < 1.0 were also seen for all categories of time since start of use and for cumulative calls. Study participants who first used a mobile phone at least 10 years before interview did not show an increased risk of meningioma. Regarding cumulative number of calls, the group with highest exposure did not show an increased risk of glioma or meningioma. In terms of cumulative call time, all odds ratios were < 1.0 for all deciles of exposure except the highest (10th) decile of recalled cumulative call time (≥ 1640 hours). For this exposure group, the odds ratio for meningioma was 1.15 (95% CI, 0.81–1.62). Increased risk in the highest exposure decile of cumulative call time was more pronounced in short-term users, who started to use phones 1–4 years before the reference date, than in long-term users (≥ 10 years). Sensitivity analyses had little effect on estimated associations between mobile-phone use and risk of meningioma.

The analysis of TCSE and risk of meningioma in five INTERPHONE countries (Cardis *et al.*, 2011) was based on 674 cases of meningioma and 1796 controls. In the highest quintile of TCSE, the odds ratio for meningioma was 0.90 (95% CI, 0.66–1.24). An odds ratio of 1.01 (95% CI, 0.75–1.36) was reported for the highest quintile of cumulative call time without hands-free devices. In terms of TCSE exposure ≥ 7 years before the reference date, there was no consistent dose–response pattern, but the odds ratio was elevated in the quintile of highest exposure (OR, 2.01; 95% CI, 1.03–3.93). In case-only analyses, the

Table 2.14 Case–control studies of meningioma and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (1999) Sweden, 1994–96	46	439	Population, matched on sex, age, region, and year of diagnosis	Self-administered standardized questionnaire	Meningioma	Never use of mobile phone	30	1.0		
						Ever use	16	1.0 (0.5–2.3)		
Inskip *et al.* (2001) Phoenix, Boston, Pittsburgh, 1994–98.	197	799	Patients admitted to the same hospitals for a variety of non-malignant conditions.	Computer-assisted, personal interview in the hospital	Meningioma	Regular use	32	0.8 (0.4–1.3)	Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	There are results for other exposure metrics: average daily use, duration, year use began. Also results for laterality.
						Duration ≥ 5 yr	6	0.9 (0.3–2.7)		
						Cumulative use (h)				
						Never or rarely used	165	1.0		
						< 13	8	0.7 (0.3–1.9)		
						13–100	13	1.1 (0.5–2.4)		
						> 100	11	0.7 (0.3–1.7)		
						> 500	6	0.7 (0.2–2.4)		
Auvinen *et al.* (2002) Finland, 1996	398 (129 meningiomas)	1990	Population Registry Centre of Finland	Information on subscriptions obtained from the two mobile-network providers operating in Finland in 1996	Meningioma (225.2)	*Analogue*			Age, sex	Cases aged 20–69 yr
						Ever	8	1.5 (0.6–3.5)		
						< 1 yr	3	2.3 (0.6–9.2)		
						1–2 yr	3	1.6 (0.4–6.1)		
						> 2 yr	2	1.0 (0.2–4.4)		
						Digital				
						Ever	3	0.7 (0.2–2.6)		

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2006a) Sweden, 1997–2003	916	2162	Population.	Self-administered questionnaire	Meningioma	Never used mobile or cordless phone	455	1.0	Age, sex, SEI, year of diagnosis	Ipsilateral use of analogue and digital phones was associated with meningioma (analogue: OR, 1.3; 95% CI, 0.9–2.0; digital: OR, 1.4; 95% CI, 1.0–1.8), contralateral use was not (OR, 1.2; 95% CI, 0.7–1.8; and OR, 1.1; 95% CI, 0.8–1.5, respectively).
						Cumulative use, analogue (h)				
						1–500	99	1.3 (1.0–1.7)		
						501–1000	8	1.1 (0.5–2.6)		
						> 1000	6	1.4 (0.5–3.8)		
						Cumulative use, digital (h)				
						1–500	268	1.1 (0.9–1.3)		
						501–1000	18	1.0 (0.6–1.8)		
						> 1000	9	0.7 (0.3–1.4)		
						Latency, analogue (yr)				
						> 1–5	32	1.2 (0.8–1.8)		
						> 5–10	47	1.2 (0.8–1.8)		
						> 10	34	1.6 (1.0–2.5)		

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
INTERPHONE Study Group (2010) Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, United Kingdom, 2000–04	2409	2662	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Meningioma (D32.0, D32.9, D42.0, D42.9, C70.0, C70.9)	Never regular use of mobile phone	1147	1.00	Sex, age, study centre, ethnicity (in Israel), and education	
						Ever use	1262	0.79 (0.68–0.91)		
						Time since start of use (yr)				
						1–1.9	178	0.90 (0.68–1.18)		
						2–4	557	0.77 (0.65–0.92)		
						5–9	417	0.76 (0.63–0.93)		
						≥ 10	110	0.83 (0.61–1.14)		
						Cumulative call time with no hands-free devices (h)				OR, 4.80 (95% CI, 1.49–15.4) in short-term users (start of mobile-phone use 1–4 yr before reference date) with cumulative call time ≥ 1640 h (based on 22 cases)
						< 5	160	0.90 (0.69–1.18)		
						5–12.9	142	0.82 (0.61–1.10)		
						13–30.9	144	0.69 (0.52–0.91)		
						31–60.9	122	0.69 (0.51–0.94)		
						61–114.9	129	0.75 (0.55–1.00)		
						115–199.9	96	0.69 (0.50–0.96)		
						200–359.9	108	0.71 (0.51–0.98)		
						360–734.9	123	0.90 (0.66–1.23)		
						735–1639.9	108	0.76 (0.54–1.08)		
						≥ 1 640	130	1.15 (0.81–1.62)		

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Cardis *et al.* (2011) Australia, Canada, France, Israel, Italy, New Zealand, 2000–04	674	1796	Population	Interviewer-administered standardized questionnaire	Meningioma	*RF TCSE (J/kg)*			Sex, age, study centre, ethnicity (in Israel) and education	Interpretation of OR is most meaningful when compared with the corresponding OR for comparable exposure surrogates of mobile-phone use
						Never regular user	294	1.0		Subjects with tumour centre estimated by a neuro-radiologist or by means of a computer algorithm
						< 76.7	103	0.90 (0.67–1.21)		
						76.7-	71	0.74 (0.53–1.04)		Exposure ≥ 7 yr before reference date: OR, 2.01 (95% CI, 1.03–3.93), for highest quintile
						284.1-	56	0.56 (0.39–0.80)		
						978.9-	62	0.72 (0.51–1.02)		
						3123.9+	88	0.90 (0.66 to 1.24)		

h, hour; OR, odds ratio; RF, radiofrequency radiation; SEI, socioeconomic index; TCSE, total cumulative specific energy; yr, year

odds ratio for having the centre of the tumour within the most exposed area was 1.34 (95% CI, 0.55–3.25) in those who reported starting to use a mobile phone ≥ 10 years previously.

Hardell *et al.* (2006a) reported the results of a pooled analysis of case–control studies of benign tumours of the brain and use of mobile and cordless phones that included 1254 cases of benign tumours, of which 916 were meningioma; deceased cases (and controls) were not included in this analysis. An odds ratio of 1.3 (95% CI, 0.99–1.7) was reported for meningioma when users of analogue mobile phones were compared with people who reported no use of mobile or cordless phones, or exposure ≤ 1 year before the reference date. The odds ratio was 1.1 (95% CI, 0.9–1.3) for users of digital mobile phones and 1.1 (95% CI, 0.9–1.4) for users of cordless phones. Study participants who first used an analogue, digital, or cordless phone at least 10 years previously showed increased risks of meningioma, although estimates were imprecise (OR, 1.6; 95% CI, 1.0–2.5; OR, 1.3; 95% CI, 0.5–3.2; OR, 1.6; 95% CI, 0.9–2.8, respectively).

(iii) Acoustic neuroma

See Table 2.15

Inskip *et al.* (2001) included a total of 96 cases with acoustic neuroma and 799 controls. Compared with non-users, self-reported regular users of mobile phones did not manifest excess risks of acoustic neuroma (OR, 1.0; 95% CI, 0.5–1.9).

A case–control study of 90 cases of acoustic neuroma and 86 controls selected from among other patients was conducted in a hospital in New York (Muscat *et al.*, 2002). Subjects were interviewed regarding use of mobile phones and other factors. Analysis of reported histories of mobile-phone use, adjusting for sociodemographic factors and date of interview, yielded a set of odds-ratio estimates that were close to the null value for cumulative hours of use and years of use. [The Working Group noted that numbers were small, exposure levels were low, and time since first use was short.]

Schoemaker *et al.* (2005) reported pooled results on acoustic neuroma from a subset of the INTERPHONE countries (the five north European countries: Denmark, Finland, Norway, Sweden, and the United Kingdom). There was no indication of an increased risk of acoustic neuroma associated with mobile-phone use (Table 2.15). Similar negative findings were reported by the INTERPHONE groups in France (Hours *et al.*, 2007) and Germany (Schlehofer *et al.*, 2007), and from a case–control study in Japan (Takebayashi *et al.*, 2006).

In Japan, Sato *et al.* (2011) identified a series of cases of acoustic neuroma diagnosed between 2000 and 2006 in 22 participating hospitals with neurosurgery departments (32% of hospitals solicited). Of 1589 cases identified, 816 agreed to respond to a self-administered questionnaire, received by post, focusing on history of mobile-phone use and history of pre-diagnosis symptoms. Two case series were constituted consisting of: (a) 180 cases among mobile-phone users whose symptoms had not appeared 1 year before diagnosis; and (b) 150 cases among mobile-phone users whose symptoms had not yet appeared 5 years before diagnosis. In each series, the investigators then compared laterality of the tumour with laterality of mobile-phone use and, using a formula described by Inskip *et al.* (2001), they derived an estimate of relative risk of acoustic neuroma related to various metrics of mobile-phone use. Overall, there was no excess risk of acoustic neuroma among ever-users of mobile phones. However, among some subgroups, namely those with the highest duration of daily calls, there were estimates of high risk ratios in the range of 2.74 (95% CI, 1.18–7.85) to 3.08 (95% CI, 1.47–7.41). This excess appeared to be restricted to a small group of cases who were persistently among the highest users during the past 5 years. The authors considered various alternative explanations for this finding,

Table 2.15 Case–control studies of acoustic neuroma and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Inskip *et al.* (2001) USA, 1994–98	96	799	Patients admitted to the same hospitals for a variety of non-malignant conditions	Computer-assisted personal interview in the hospital	Acoustic neuroma	Regular use Duration ≥ 5 yr	22 5	1.0 (0.5–1.9) 1.9 (0.6–5.9)	Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	Analyses by cumulative use showed no associations. Analyses of laterality of tumour by laterality of phone use showed no associations. Very few subjects with long-term exposure. Response rates were 92% for cases and 86% for controls. In groups with highest duration of daily calls: RR ranged from 2.74 (95% CI, 1.18–7.85) to 3.08 (95% CI, 1.47–7.41)
Muscat *et al.* (2002) New York City, 1997–99	90	86	In-patients with non-malignant conditions from the same hospitals	Interviews with structured questionnaire	Acoustic neuroma (225.1)	Cumulative use (h): 0 1–60 > 60 Years of use: 0 1–2 3–6	 72 9 9 72 7 11	 1.0 0.9 (0.3–3.1) 0.7 (0.2–2.6) 1.0 0.5 (0.2–1.3) 1.7 (0.5–5.1)	Age, education, sex, study centre, occupation categories, and date of interview	Also presented as h/mo, with similar results. In mobile-phone users tumour was most often on contralateral side.

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Schoemaker *et al.* (2005) Denmark, Finland, Norway, Sweden, United Kingdom, 1999–2004	678	3553	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone	316	1.0	Educational level and combinations of interview year and interview lag time	Matched for centre, region, 5-yr age group, sex
						Regular use	360	0.9 (0.7–1.1)		
						Time since start of use (yr)				
						1.5–4	174	0.8 (0.7–1.0)		
						5–9	139	0.9 (0.7–1.2)		
						≥ 10	47	1.0 (0.7–1.5)		
						P for trend		0.9		
						Cumulative use (h)				
						< 116	168	0.9 (0.7–1.1)		
						116–534	89	0.9 (0.7–1.2)		
						> 534	94	0.9 (0.7–1.2)		
						P for trend		0.5		
Takebayashi *et al.* (2006) Japan, 2000–04	101	339	Population (random-digit dialling)	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone	46	1.0	Education, marital status	Matched for age, sex, residency
						Regular use	51	0.73 (0.43–1.23)		
						Time since start of use (yr)				
						< 4	26	0.70 (0.39–1.27)		
						4–7	21	0.76 (0.38–1.53)		
						≥ 8	4	0.79 (0.24–2.65)		
						P for trend		0.70		
						Cumulative use (h)				
						< 300	35	0.67 (0.38–1.17)		
						300–900	9	1.37 (0.54–3.50)		
						> 900	7	0.67 (0.25–1.83)		
						P for trend		0.69		

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Ha *et al.* (2007) France, 2001–03	109	214	Population (electoral rolls)	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone	51	1.0	SES, tobacco consumption, noise exposure	Sex, age (± 5 yr), place of residence
						Regular use	58	0.92 (0.53–1.59)		
						Duration of use (mo)				
						< 16	19	1.21 (0.55–2.69)		
						16–27	17	1.33 (0.58–3.03)		
						27–46	8	0.63 (0.26–1.53)		
						> 46	14	0.66 (0.28–1.57)	OR per 1 year, 0.96 (0.84–1.10)	
						Cumulative use (h)				
						< 20	14	1.06 (0.48–2.36)		
						20–80	15	0.87 (0.40–1.91)		
						80–260	13	0.85 (0.38–1.88)		
						> 260	16	0.92 (0.41–2.07)	OR per 80 h, 1.0 (0.96–1.03)	
Schlehofer *et al.* (2007) Germany, 1976–88	97	194	Population	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone	68	1.0	SES, urbanity	Matched for centre, age, sex
						Regular use	29	0.67 (0.38–1.19)		
						Time since start of use (yr)				
						1–4	20	0.78 (0.40–1.50)		
						5–9	8	0.53 (0.22–1.27)		
						≥ 10	0	-		
						Cumulative use (h)				
						< 44	16	1.04 (0.51–2.16)		
						44–195	7	0.58 (0.22–1.48)		
						> 195	5	0.35 (0.12–1.01)		

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Sato *et al.* (2011) Japan, 2000–06	787	787 (case–case)	Note: the affected ear is the case side; the opposite ear is regarded as the control.	Mailed questionnaire about history of mobile-phone use	Acoustic neuroma	Overall, for regular mobile-phone use until one yr before diagnosis	180	1.08 (0.93–1.28)	Same patients	The authors interpret these significant results with caution, mentioning detection and recall bias as possibilities.
						Overall, for regular mobile-phone use until 5 yr before diagnosis	150	1.14 (0.96–1.40)		
						Weighted daily average call duration > 20 min, 1 yr before diagnosis	23	2.74 (1.18–7.85)		
						Weighted daily average call duration > 20 min, 5 yr before diagnosis	33	3.08 (1.47–7.41)		

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
INTERPHONE Study Group (2011) Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, United Kingdom, 2000–04	1105	2145	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Schwannoma of the acoustic nerve (ICD-9 code 225.1 or ICD-10 code D33.3, and ICD-O topography code C72.4 and morphology code 9560/0)	Never regular use of mobile phone	801	1.00	Sex, age, study centre, ethnicity (in Israel), and education	Data are given only for exposure up to 5 yr before reference date (risk estimates were generally smaller when exposure up to 1 yr before reference date was considered)
						Regular use	304	0.95 (0.77–1.17)		
						Time since start of use (yr)				
						5–9	236	0.99 (0.78–1.24)		
						≥ 10	68	0.83 (0.58–1.19)		
						Cumulative call time (h) with no hands-free devices				When stratifying for duration of use, OR was highest in long-term users (start of mobile-phone use ≥ 10 yr ago): OR, 1.93 (95% CI, 1.10–3.38). Ipsilateral use: OR, 3.74 (95% CI, 1.58–8.83); contralateral use: OR, 0.48 (95% CI, 0.12–1.94)
						< 5	42	1.07 (0.69–1.68)		
						5–12.9	30	1.06 (0.60–1.87)		
						13–30.9	40	1.32 (0.80–2.19)		
						31–60.9	36	0.86 (0.52–1.41)		
						61–114.9	21	0.63 (0.35–1.13)		
						115–199.9	22	0.71 (0.39–1.29)		
						200–359.9	49	0.83 (0.48–1.46)		
						360–734.9	26	0.74 (0.42–1.28)		
						735–1639.9	22	0.60 (0.34–1.06)		
						≥ 1640	32	2.79 (1.51–5.16)		

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2006a) Sweden, 2000–03	243		Population	Self-administered standardized questionnaire	Acoustic neuroma	Never use of mobile or cordless phone	88	1.0	Age, sex, SEI, and year of diagnosis	
						Ever use of analogue phone	68	2.9 (2.0–4.3)		
						Ever use of digital phone	105	1.5 (1.1–2.1)		
						Ever use of cordless phone	96	1.5 (1.0–2.0)		
						Cumulative call time, analogue (h)				
						1–500	55	2.8 (1.8–4.2)		
						501–1000	7	3.3 (1.3–8.0)		
						> 1000	6	5.1 (1.9–14)		
						Cumulative call time, digital (h)				
						1–500	83	1.4 (1.0–2.0)		Users of analogue phone (> 10 yr) showed OR, 3.1 (95% CI, 1.7–5.7)
						501–1000	10	1.8 (0.8–3.8)		
						> 1000	12	3.1 (1.5–6.4)		
						Cumulative call time, cordless (h)				
						1–500	60	1.3 (0.9–1.9)		
						501–1000	15	1.6 (0.9–3.0)		
						> 1000	21	2.1 (1.2–3.7)		

GP, general practitioner; h, hour; min, minute; mo, month; OR, odds ratio; SEI, socioeconomic index; SES, socioeconomic status; yr, year

including selection bias and recall bias, and they concluded that it was unclear whether the finding was a consequence of bias.

The pooled INTERPHONE analysis for acoustic neuroma (INTERPHONE Study Group, 2011) followed in general the same methodology as the analyses for glioma and meningioma described above (INTERPHONE Study Group, 2010). Patients diagnosed with a schwannoma of the acoustic nerve in the study regions during study periods of 2–4 years between 2000 and 2004 were included in the study. For each case, two age-, sex- and study-region-matched controls were recruited. Controls were either specifically sampled for the cases of acoustic neuroma, taken from the pool of INTERPHONE controls drawn for all tumours together, or obtained with a combination of both approaches. In total, 1105 cases (participation rate, 82%) were included in the analyses, together with 2145 controls (participation rate, 53%). The odds ratio for regular use was 0.85 (95% CI, 0.69–1.04) when recording exposure at 1 year before the reference date and 0.95 (95% CI, 0.77–1.17) when recording exposure at 5 years before the reference date. For cumulative call time, the highest odds ratios were observed in the highest category of use: the odds ratios for ≥ 1640 hours were 1.32 (95% CI, 0.88–1.97) when recording exposure at 1 year and 2.79 (95% CI, 1.51–5.16) when recording exposure at 5 years. There was, however, no consistent trend in the exposure–response relationship in the first nine deciles of exposure. Stratifying the analyses according to time since start of mobile-phone use resulted in an increased odds ratio for heavy users of mobile phones only in long-term users (OR, 1.93; 95% CI, 1.10–3.38, based on 37 cases). This risk estimate was more pronounced with respect to ipsilateral use (OR, 3.74; 95% CI, 1.58–8.83, based on 28 cases) and decreased with respect to contralateral use (OR, 0.48; 95% CI, 0.12–1.94, based on 4 cases). Exclusion of participants with an implausible amount of use (> 5hours per day) resulted in a decrease in odds ratio for exposure up to 1 year before the reference date, but had little impact on the results of the analyses of exposure up to 5 years before the reference date. The results for cumulative number of calls were broadly similar, but risk estimates were smaller.

Overall, these results were broadly similar to the results for glioma from the INTERPHONE study. [The same methodological limitations were of concern, mainly selection and recall bias. Diagnostic bias was also of concern: patients with acoustic neuroma who use mobile phones may be diagnosed earlier than non-users, since acoustic neuroma affects hearing capability. However, such an effect would be expected to be most relevant for recent users, but of little relevance for exposure 5 years before diagnosis. On the other hand, prodromal symptoms might discourage cases from becoming mobile-phone users. Again, such an effect would be most relevant in the analysis of most recent use of mobile phones, but not in the analysis of exposure at earlier dates. There is also uncertainty as to how early symptoms may affect the preferred side of use. Regarding confounding, socioeconomic status, ionizing radiation and loud noise were considered, with little effect on the results.]

Hardell *et al.* (2006a) reported the results of a pooled analysis of associations between use of mobile and cordless phones and risk of benign tumours of the brain that included 243 cases of acoustic neuroma. An increased odds ratio was reported for acoustic neuroma (OR, 2.9; 95% CI, 2.0–4.3) when users of analogue mobile phones were compared with people who reported no use of mobile or cordless phones, or exposure ≤ 1 year before the reference date. The odds ratio was 1.5 (95% CI, 1.1–2.1) for users of digital mobile phones and 1.5 (95% CI, 1.04–2.0) for users of cordless phones. Study participants who first used an analogue phone at least 10 years before the reference date showed increased risks (OR, 3.1; 95% CI, 1.7–5.7), but users of digital or cordless phones did not. For users of analogue mobile phones, an increased odds ratio was

seen for ipsilateral use (OR, 3.0; 95% CI, 1.9–5.0) and contralateral use (OR, 2.4; 95% CI, 1.4–4.2) when compared with people who had not used mobile or cordless phones. For users of digital mobile phones, an increased odds ratio was seen for acoustic neuroma with ipsilateral use (OR, 1.7; 95% CI, 1.1–2.6), but not for contralateral use (OR, 1.3; 95% CI, 0.8–2.0) when compared with people who had not used mobile or cordless phones. Similar associations were found for use of cordless phones (ipsilateral use: OR, 1.7; 95% CI, 1.1–2.6; and contralateral use: OR, 1.1; 95% CI, 0.7–1.7, respectively) (Schüz *et al.*, 2006c).

(iv) All cancers of the brain combined

See Table 2.16

In several studies already referred to above, analyses were presented for all cancers of the brain combined (Hardell *et al.*, 2000, 2001, 2011a; Inskip *et al.*, 2001; Auvinen *et al.*, 2002). Only in Hardell *et al.* (2011a) were risks of cancer significantly elevated with prolonged use of mobile phones. A study in France by Spinelli *et al.* (2010) found no significant excess risks.

(v) Other cancers of the brain

A pooled analysis by Hardell *et al.* (2011a) included 103 cases with a histopathological diagnosis of malignant tumour of the brain other than glioma. Odds ratios for malignant tumours other than glioma by category of duration of mobile-phone use were 1.0 (95% CI, 0.6–1.6) for 1–1000 hours, 1.4 (95% CI, 0.4–4.8) for 1001–2000 hours, and 1.2 (95% CI, 0.3–4.4) for > 2000 hours.

(vi) Pituitary tumours

See Table 2.17

In a Japanese study, 102 cases of pituitary adenoma were included, together with 161 individually matched controls (Takebayashi *et al.*, 2008). Neither regular use of mobile phones (OR, 0.90; 95% CI, 0.50–1.61) nor cumulative duration of use in years and cumulative call time in hours was associated with an increased risk of pituitary tumours.

In a population-based case–control study from south-eastern England, 291 cases of pituitary tumour diagnosed between 2001 and 2005 were included, together with 630 controls that were frequency-matched for sex, age, and health-authority of residence (Schoemaker & Swerdlow, 2009). The participation rate was 63% for cases and 43% for controls. Data were collected with a face-to-face interview at the subject's home or another convenient place. Regular use was not associated with an increased risk (OR, 0.9; 95% CI, 0.7–1.3) nor was any other exposure surrogate. Stratified analyses for analogue or digital mobile-phone user did not indicate consistent exposure–response associations.

(d) Some reviews, meta-analyses, and other studies

Various meta-analyses and other comparisons of the accumulating data on mobile-phone use and tumours of the brain have been published (Hardell *et al.*, 2003, 2007a, 2008; Lahkola *et al.*, 2006; Kan *et al.*, 2008; Ahlbom *et al.*, 2009; Hardell & Carlberg, 2009; Khurana *et al.*, 2009; Myung *et al.*, 2009). Such analyses are potentially useful for characterizing the accumulating evidence and for exploring heterogeneity of findings among studies, along with determinants of any observed heterogeneity. [The Working Group based its conclusions on review of the primary studies.]

2.3.2 Leukaemia and lymphoma

(a) Leukaemia

There have been four epidemiological studies on leukaemia and use of mobile phones.

In an early cohort study of 285 561 users of analogue phones, identified based on records from two mobile-phone providers in the USA in 1993, mortality attributable to leukaemia was not elevated among users of hand-held phones relative to users of non-hand-held phones (mostly car phones) (Dreyer *et al.*, 1999; Table 2.18). [A

Table 2.16 Case–control studies of all cancers of the brain and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2000, 2001) Uppsala-Orebro region and Stockholm region, Sweden, 1994–96	209 cases of brain tumours diagnosed 1994–96 among people aged 20–80 yr at diagnosis	425	Population register. 1:2 case:control ratio with matching on age and sex, and drawn from the same geographical areas as the cases	Self-administered structured, mailed questionnaire	All malignant tumours of the brain. Benign tumours of the brain included from Stockholm in 1996, as part of feasibility study. Histopathology reports on 197 patients, 136 with malignant and 62 with benign tumours.	No use of mobile or cordless phone, or exposure ≤ 1 yr before reference date Mobile-phone use	 78	1 0.98 (0.69–1.41)	Sex, age (as a continuous variable). Radiotherapy, diagnostic X-ray, asbestos, solvents, smoking	Participation rate was 90% for cases and 91% for controls. Increased risk for tumour in the temporal or occipital lobe on same side as cell-phone use (OR, 2.62; 95% CI, 1.02–6.71). Contralateral use did not increase the risk (OR, 0.97; 95% CI, 0.36–2.59). Deceased cases were not included. This analysis encompassed the case–control data included in Hardell *et al.* (2000)
Inskip *et al.* (2001) USA, 1994–98	782	799	Patients admitted to the same hospitals for a variety of non-malignant conditions.	Computer-assisted in person interview in the hospital, history of mobile-phone use	All brain	No use Regular use Duration ≥ 5 yr	471 139 22	1.0 0.8 (0.6–1.1) 0.9 (0.5–1.6)	Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	Analyses by cumulative use showed no associations. Very few subjects with long-term exposure. Response rates 92% for cases and 86% for controls.

Table 2.16 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Auvinen *et al.* (2002) Finland, 1996	398	1990	Population Registry Centre of Finland	Information on subscriptions obtained from the two mobile-network providers operating in Finland in 1996	All brain (191 and 225.2)	*Analogue*			Age, sex	Cases aged 20–69 yr
						Ever	40	1.6 (1.1–2.3)		
						< 1 yr	8	1.6 (0.7–3.6)		
						1–2 yr	15	1.5 (0.9–2.8)		
						> 2 yr	17	1.6 (0.9–2.8)		
						Digital				
						Ever	16	0.9 (0.5–1.5)		
						< 1 yr	4	0.6 (0.2–1.6)		
						1–2 yr	11	1.2 (0.6–2.3)		
						> 2 yr	1	0.6 (0.1–4.5)		
Spinelli *et al.* (2010) France, 2005	122	122	In-patients from neurosurgery departments of the same hospitals; unrelated to cancer	Face-to-face interviews with standardized questionnaire; and self-administered questionnaire	Malignant primary tumours of the brain	*Global cellular-phone use (hours-year)*			Age, sex	
						0	37	1		
						≤ 4	8	0.86 (0.30–2.44)		
						4–36	58	1.45 (0.75–2.80)		
						≥ 36	13	1.07 (0.41–2.82)		

Table 2.16 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2011a)	1251 cases of malignant brain tumours diagnosed during 1997–2003 among people aged 20–80 yr at diagnosis	2438 controls	Population register. 1:1 case:control ratio with matching on age and sex, and drawn from the same region as the cases. For deceased cases, controls drawn from death registry. 1:1 matching on year of death, sex, age, and medical region	Self-administered structured, mailed questionnaire. For deceased cases and controls, mailed questionnaire was completed by relative of decedent.	All malignant tumours of the brain	No use of mobile or cordless phone, or exposure ≤ 1 yr before reference date	677	1.00	Sex, age (as a continuous variable), SEI code, year of diagnosis	Participation rates were 85% for cases and 84% for controls. This analysis encompassed the data presented in earlier papers on pooled case–control studies of malignant tumours of the brain among living cases diagnosed in 1997–2003
						Mobile-phone use:				
						Ever	574	1.3 (1.1–1.5)		
						1–1000 h	466	1.2 (1.0–1.4)		
						1001–2000 h	47	1.8 (1.1–2.7)		
						> 2000 h	61	3.0 (1.9–4.8)		
					Malignant tumours of the brain other than glioma (*n* = 103)	Mobile-phone use:				
						1–1000 h	39	1.0 (0.6–1.6)		
						1001–2000 h	3	1.4 (0.4–4.8)		
						> 2000 h	3	1.2 (0.3–4.4)		

h, hour or hours; SEI, socioeconomic index; yr, year

Table 2.17 Case–control studies of cancers of the pituitary and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Takebayashi *et al.* (2008) Japan, 2000–04	101	161	Population (random-digit dialling)	Interviewer-administered standardized questionnaire	Pituitary adenoma (ICD code not reported)	Never regular use of mobile phone	39	1.0	Education, marital status	Matched for age (5 yr), sex, residency
						Regular use	62	0.90 (0.50–1.61)		
						Time since start of use (yr)				
						< 2.2	14	0.86 (0.39–1.88)		
						2.2–4.69	13	0.75 (0.31–1.81)		
						4.7–6.5	22	1.64 (0.74–3.66)		
						> 6.5	13	0.75 (0.31–1.82)		
						P for trend		0.89		
						Cumulative use (h)				
						< 39	15	1.00 (0.46–2.16)		
						39–190	14	0.97 (0.40–2.32)		
						190–560	12	0.72 (0.31–1.70)		
						> 560	21	1.33 (0.58–3.09)		
Schoemaker & Swerdlow (2009) United Kingdom, 2001–05	291	630	Population (from GP patient list)	Interviewer-administered standardized questionnaire	Pituitary tumour (C75.1, D35.2, D44.3)	Never regular use of mobile phone	116	1.0	Age, sex, category, geographic area, reference date, and Townsend deprivation score	
						Regular use	175	0.9 (0.7–1.3)		
						Time since start of use (yr)				
						1.5–4	89	1.0 (0.7–15)		
						5–9	62	0.8 (0.5–1.2)		
						10–17	24	1.0 (0.5–1.9)		
						P for trend		0.7		
						Cumulative use (h)				
						< 113	79	0.9 (0.6–1.3)		
						113–596	44	1.1 (0.7–1.8)		
						> 596	51	1.1 (0.7–1.7)		
						P for trend		0.9		

GP, general practitioner; h, hour or hours; yr, year

limitation of this study was that there were only four deaths due to leukaemia among users of hand-held phones, as the study was truncated – with no access to mortality data beyond 1 year – as a result of a legal proceeding.]

A study of cancer incidence in a cohort of 420 095 users of mobile phones in Denmark found no evidence of an elevated risk of leukaemia in males or females (SIR, 1.05; 95% CI, 0.96–1.15) (Schüz *et al.*, 2006c; Table 2.18). The incidence of leukaemia was not increased in any of the reported time intervals since first subscription. Details concerning the design of the study were discussed above (Section 2.3.1). [The results for leukaemia were not reported separately by subtype.]

A hospital-based case–control study of adult-onset leukaemia in Thailand conducted between 1997 and 2003 (180 cases, 756 hospital controls) reported an odds ratio for all leukaemias combined of 1.5 (95% CI, 1.0–2.4) (Kaufman *et al.*, 2009; Table 2.19). Overall, the duration of mobile-phone use was short (median, 24–26 months). The results were similar for acute myeloid leukaemia, chronic myeloid leukaemia and chronic lymphocytic leukaemia. There were no trends in associations of all leukaemias with duration of ownership, lifetime hours of use, or amount of use per year. The odds ratio was highest for persons reporting exclusive use of GSM (Global System for Mobile Communications) services. Using an categorization ad hoc into "high risk" and "low risk" groups of mobile-phone users based on phone characteristics, the authors reported an odds ratio of 1.8 for high-risk versus low-risk users (95% CI, 1.1–3.2). [It was unclear to the Working Group as to how the "high risk" and "low risk" groups were derived and whether it was done *a priori* or *a posteriori*.]

In a study conducted in the United Kingdom between 2003 and 2009, which included 806 cases and 585 controls who were non-blood relatives, regular use of a mobile phone (defined as at least one call per week for at least 6 months) was not associated with the incidence of leukaemia (Cooke *et al.*, 2010; Table 2.19). Risk was not significantly associated with years since first use, lifetime years of use, cumulative number of calls, or cumulative hours of use. Among people who reported using a phone for ≥ 15 years since first use, the odds ratio was 1.87 (95% CI, 0.96–3.63; 50 exposed cases); however, there was no apparent trend with years since first use. There also was no apparent trend in risk with cumulative hours of use. Findings were similar for digital and analogue phones. There was no apparent variation in results by subtype of leukaemia and no trend in risk with years since first use, years of use, or cumulative hours of use for any subtype. [Only 50% of potential cases participated, with the usual reasons for non-participation being death or disability related to leukaemia.]

(b) Lymphoma

In a population-based case–control study conducted in Sweden between 1999 and 2002 (910 cases, 1016 controls), neither mobile-phone use nor cordless-phone use was significantly associated with risk of NHL overall, nor for the B-cell subtype in particular (90% of the cases) (Hardell *et al.*, 2005; Table 2.19). High odds ratios were reported for some categories of use of cordless phones for T-cell lymphomas, based on very small numbers. Cases in this study were diagnosed between the ages of 18 and 74 years. Males and females were included, but the main results concerning mobile-phone use were presented for both sexes combined.

A population-based case–control study of NHL conducted in the USA between 1998 and 2000 (551 cases, 462 controls) also reported predominantly null findings (Linet *et al.*, 2006; Table 2.19). Several exposure metrics of mobile-phone use were presented (latency, duration, amount of exposure), but overall there was no consistent trend in risk. Risk of NHL was not associated with minutes per week of use of mobile telephones, duration of use, cumulative

Table 2.18 Cohort studies of leukaemia, lymphoma, and other cancers, and use of mobile phones

Reference, study location and period	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Dreyer *et al.* (1999) USA, 1993	285 561	1993	Records of mobile-phone service providers	Leukaemia (204–207)	*Hand-held phones* < 2 min/d ≥ 2 min/d	 2 2	*SMR* 1.6 4.9	Age, sex, metropolitan area	Mortality study; effect estimate = SMR; SMR for non-hand-held phones (non-exposed), 7.0
Schüz *et al.* (2006c) Denmark, 1982–2002	420 095	1982–2002	Records of mobile-phone service providers	Leukaemia (204–207)	*Latency (yr)* < 1 1–4 5–9 ≥ 10	 33 151 135 32	*SIR* 1.09 (0.75–1.52) 1.05 (0.90–1.24) 0.92 (0.77–1.08) 1.08 (0.74–1.52)	Age, sex, calendar period of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available
Schüz *et al.* (2006c) Denmark, 1982–2002	65 542	1982–2002	Records of cellular service providers	Female breast (174)	Subscriber	711	1.04 (0.97–1.12)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available
Schüz *et al.* (2006c) Denmark, 1982–2002	420 095	1982–2002	Records of cellular service providers	Eye (190)	Subscriber	38 (males) 6 (females)	0.94 (0.66–1.29) 1.10 (0.40–2.39)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available

Table 2.18 (continued)

Reference, study location and period	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Schüz *et al.* (2006c) Denmark, 1982–2002	357 553	1982–2002	Records of cellular service providers	Testis (186)	Subscriber	522	1.05 (0.96–1.15)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available
Schüz *et al.* (2006c) Denmark, 1982–2002	420 095	1982–2002	Records of cellular service providers	Salivary gland (142)	Subscriber	26 (males) 0 (females)	0.86 (0.56–1.26) 0.00 (0.00–1.02)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available

d, day; h, hour; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year

lifetime use, nor year of first use. The incidence of NHL was elevated among men who had used cell phones for > 8 years (OR, 2.4; 95% CI, 0.8–7.0, based on 17 cases).

2.3.3 Uveal (ocular) melanoma

In a study of 118 cases and 475 controls, Stang *et al.* (2001) reported an association between assessed occupational use of mobile phones and risk of uveal melanoma (Table 2.19). Methods for this study are described in greater detail in Section 2.1.3. [There was no adjustment for exposure to ultraviolet radiation, which may be a relevant confounder. Exposure information was crude, and concerns were raised about possible bias in the self-reported data in this small study (Johansen *et al.*, 2002).]

The same investigators carried out a much larger case–control study (455 cases; aged 20–74 years) between 2002 and 2004 using a more refined exposure-assessment instrument (Stang *et al.*, 2009; Table 2.19). Three control series were enrolled. One included 827 population controls selected from census data from local districts and matched to case patients on age (5-year age groups), sex and region of residence. A second control series included 180 ophthalmology patients – recruited from practices of the same ophthalmologists who had referred the case patients with uveal melanoma – who had a newly diagnosed benign disease of the eye. The third control group consisted of 187 siblings of cases. Participation rates were 94% for the case patients, 57% for the population and sibling control subjects, and 52% for the ophthalmologists control subjects. The risk of uveal melanoma was not associated with regular use of mobile phones based on any of the three control series (with population controls: OR, 0.7; 95% CI, 0.5–1.0; with ophthalmologist controls: OR, 1.1; 95% CI, 0.6–2.3; and with sibling controls: OR, 1.2 95% CI, 0.5–2.6). There were no associations with cumulative measures of exposure (years of use, number of calls) based on any of the control series. [The Working Group noted the higher participation rate for cases than for controls and the attendant possibility of selection bias.]

The incidence of cancer of the eye (histology not specified, but likely to include a high proportion of melanomas) was not increased in a large cohort of Danish mobile-phone subscribers relative to the general population in a study that reported follow-up until 2002 (Schüz *et al.*, 2006c; Table 2.18).

The substantial increase in use of mobile telephones has not been accompanied by an increase in uveal (ocular) melanoma in the USA up to 2000 (Inskip *et al.*, 2003, 2004), nor was an increase seen in Denmark up to 1996 (Johansen *et al.*, 2002). The annual percentage change in the USA was –0.7% for males (95% CI, –2.3–0.9) and –1.2% for females (95% CI, –2.5–0.0) (Inskip *et al.*, 2003). Narrowing the time window to the 1990s failed to reveal any sign of a recent increase in incidence.

2.3.4 Cancer of the testis

The potential exists for the testes to be exposed to RF radiation if a mobile phone is kept in a trouser pocket while in stand-by mode, or when using a hands-free device. The incidence of cancer of the testis was not increased among 357 533 Danish male mobile-phone subscribers relative to that in the general population, based on an average follow-up of 8 years (maximum, 21 years) (SIR, 1.05; 95% CI, 0.96–1.15) (Schüz *et al.*, 2006c; Table 2.18).

A case–control study of cell-phone use and testicular cancer in Sweden (542 seminomas, 346 non-seminomas, and 870 controls) gave null results for both histopathological subtypes (Hardell *et al.*, 2007b; Table 2.18). Cases were diagnosed between 1993 and 1997.

Table 2.19 Case–control studies of leukaemia, lymphoma and other cancers and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Kaufman *et al.* (2009) Thailand, 1997–2003	180	756	Hospital	Interviewer-administered standardized questionnaire	Leukaemia (bone marrow) (204–207)	Ever use Use of GSM services	35 NR	1.5 (1.0–2.4) 2.1 (1.1–4.0)	Matching factors age, sex, area of residence, income, exposure to benzene, solvents, pesticides, or power lines	No association with duration of ownership, lifetime hours of use, or h/yr; short duration of use (median, 24–26 months); also evaluated by subtype of leukaemia
Cooke *et al.* (2010) United Kingdom, 2003–09	806	585	Non-blood relatives	Interviewer-administered standardized questionnaire	Leukaemia (204–207) exclusive of CLL (204.1)	Never, or non-regular use Regular use Lifetime years of use: 0.5–4 5–9 10–14 ≥ 15 *P* for trend	132 674 201 309 110 42 0.30	1.00 1.06 (0.76–1.46) 0.97 (0.67–1.39) 1.10 (0.77–1.58) 1.04 (0.67–1.61) 1.63 (0.81–3.28)	Age, sex, SES, area of residence, ethnicity, smoking, interview lag-time and period	No significant associations with year since first use, lifetime years of use, cumulative number of calls, or cumulative hours of use; low participation rate (50%)
Hardell *et al.* (2005) Sweden, 1999–2002	910	1016	Population	Mail questionnaire + telephone	NHL	*Use of analogue and digital phones (yr)* > 1 > 5 > 10	 130 123 70	 1.02 (0.73–1.44) 1.04 (0.73–1.46) 0.91 (0.61–1.36)	Age, sex, year of diagnosis	Ages 18–74 yr; no differences by subtype of NHL

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Linet *et al.* (2006) USA, 1998–2000	551	462	Population	Mail + home questionnaire	NHL	Ever use	234	1.0 (0.7–1.3)	Age, ethnicity, education, geographic site	Risk also not significantly associated with min/wk, duration, or year when use started. Results were null for total NHL, large B-cell and follicular lymphoma
						Cumulative use (h):				
						≤ 78	35	0.8 (0.4–1.4)		
						79–208	23	0.8 (0.4–1.5)		
						≥ 209	35	1.1 (0.6–2.1)		
Stang *et al.* (2001) Germany, 1995–98	118	475	Population, hospital	Interview	Uveal melanoma (190)	*Probable/certain mobile-phone use*			Age, sex, geographic area	Crude exposure assessment; low prevalence of exposure; few long-term users
						Ever	6	4.2 (1.2–14.5)		
						≥ 5 yr in past	3	4.9 (0.5–51.0)		
Stang *et al.* (2009) Germany 2002–04	459	1194	Population, ophthalmology, siblings	Questionnaire	Uveal melanoma (190)			*Relative risk*	Age, sex, residence	RR estimates based on population controls; low participation rate among controls (57%)
						Regular use	30	0.7 (0.5–1.0)		
						Cumulative use (yr):				
						≤ 4	17	0.8 (0.5–1.2)		
						5–9	11	0.6 (0.4–1.0)		
						≥ 10	2	0.6 (0.3–1.4)		

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell *et al.* (2007b) Sweden 1993–97	888 (542 seminoma; 346 non-seminoma)	870	Population	Questionnaire	Testicular cancer (178)	*Cumulative use of mobile-phone (h)*			Age, year of diagnosis, cryptorchidism	Similar null results for seminoma and non-seminoma, as well as by latency
						Analogue:				
						1–127	102	1.3 (0.9–1.8)		
						128–547	46	0.7 (0.5–1.0)		
						> 547	27	0.8 (0.5–1.4)		
						Digital:				
						1–127	85	1.2 (0.8–1.8)		
						128–547	48	0.9 (0.6–1.5)		
						> 547	31	1.1 (0.6–1.9)		
Auvinen *et al.* (2002) Finland, 1996	34	170	Population	Mobile-phone subscriber lists	Salivary gland cancer (142)	Ever (analogue and digital)	4	1.3 (0.4–4.7)	Age, sex	Small number of cases; limited information on exposure; results shown are for analogue and digital phones combined
						Duration (yr):				
						< 1	0	-		
						1–2	3	1.7 (0.4–7.5)		
						> 2	1	2.3 (0.2–25.3)		
Hardell *et al.* (2004) Sweden, 1994–2000	267	1053	Population	Questionnaire	Malignant and benign salivary-gland tumours (142, 210)	Ever use (analogue)	31	0.92 (0.58–1.44)	Age, sex	Only living cases included; latency results are for analogue phones. No cases among long-term users of digital phones
						Ever use (digital)	45	1.01 (0.68–1.50)		
						Latency (yr):				
						> 5	17	0.78 (0.44–1.38)		
						> 10	6	0.71 (0.29–1.74)		

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Lönn *et al.* (2006) Denmark, Sweden, 2000–02	60	681	Population	Interviewer-administered standardized questionnaire	Malignant parotid gland (ICD codes not reported)	Never regular use of mobile phone	35	1.0	Age, sex, geographic region, education	
						Regular use	25	0.7 (0.4–1.3)		
						Time since start of use (yr)				
						< 5	14	0.7 (0.3–1.3)		
						5–9	8	0.7 (0.3–1.7)		
						≥ 10	2	0.4 (0.1–2.6)		
						Cumulative use (h)				
						< 30	7	0.7 (0.3–1.6)		
						30–449	11	0.7 (0.3–1.4)		
						≥ 450	5	0.6 (0.2–1.8)		
Lönn *et al.* (2006) Sweden, 2000–02	112	321	Population	Interviewer-administered standardized questionnaire	Benign pleomorphic adenomas (ICD codes not reported)	Never regular use of mobile phone	35	1.0	Age, sex, geographic region, education	
						Regular use	77	0.9 (0.5–1.5)		
						Time since start of use (yr)				
						< 5	47	1.0 (0.6–1.8)		Risk for ipsilateral use: OR, 1.4 (95% CI, 0.2–2.2)
						5–9	23	0.8 (0.4–1.5)		
						≥ 10	7	1.4 (0.5–3.9)		
						Cumulative use (h)				
						< 30	20	1.1 (0.6–2.3)		
						30–449	34	0.9 (0.5–1.6)		
						≥ 450	22	1.0 (0.5–2.1)		

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Sadetzki *et al.* (2008) Israel, 2001–03	460 (48 malignant; 402 benign)	1266	Population	Personal interview	Malignant and benign salivary-gland tumours (142, 210)	Not regular use of mobile phone < 1 yr	175	1.0	Unadjusted (cigarette smoking was considered but did not change OR)	Separate analyses for benign and malignant tumours, with similar results
						Regular use	285	0.87 (0.68–1.13)	Gender, interview date, age, continent of birth	Age at diagnosis, ≥ 18 yr
						Duration of use (yr)				
						1–4.9	138	0.84 (0.63–1.12)		
						5–9.9	134	0.92 (0.67–1.27)		
						≥ 10	13	1.0 (0.48–2.09)		
						Time since start of use (yr)				
						1–4.9	138	0.82 (0.61–1.10)		
						5–9.9	134	0.95 (0.70–1.30)		
						≥ 10	13	0.86 (0.42–1.77)		
						Cumulative use (h)				OR for ipsilateral use: 1.49 (95% CI, 1.05–2.13)
						≤ 266.3	121	0.82 (0.62–1.09)		
						266.4–1034.9	80	1.03 (0.72–1.47)		
						≥ 1 035	83	1.09 (0.75–1.60)		

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Duan *et al.* (2011) China 1993–2010	136	2051	Hospital	Personal or telephone interviews	Salivary-gland cancer (142)	Regular use model	91	1.14 (0.72–1.81)	Age, sex, residential area, marital status, education, income, smoking status	Possible over-parameterization; difficult to reconcile overall RR with exposure category-specific RRs
						No. of calls since first use				
						≤ 24 000	78	1.78 (1.12–2.84)	As above	Implausible RR and CI for highest exposure category (one exposed case)
						24 001–42 000	12	1.76 (1.01–2.51)		
						> 42 000	1	15.36 (13.34–17.38)		
						Duration of use (yr)				
						0–6	67	1.69 (1.05–2.73)	As above	Preceding comments raise serious questions about analysis
						7–8	7	3.69 (2.82–4.57)		
						9–10	2	7.70 (6.20–9.20)		
						> 10	15	4.14 (1.76–9.69)		

CLL, chronic lymphocytic leukaemia; GSM, Global System for Mobile Communications; min, minute; NHL, non-Hodgkin lymphoma; NR, not reported; RR, relative risk; SES, socioeconomic status; h, hour; yr, year

2.3.5 Cancers of the parotid gland

The salivary glands are potentially exposed to high doses of RF radiation from mobile phones, particularly the parotid gland on the side of the head on which the phone is used. Five case–control studies and one cohort study have addressed a possible relationship between cancer of the salivary gland and use of mobile phones.

An early case–control study by Auvinen *et al.* (2002) (Table 2.19) gave null results, but was quite small (34 cases), included only malignant tumours, and provided limited information about details of phone use. Cases were ascertained from the Finnish Cancer Registry and controls from the nationwide population registry. Personal identifiers were linked with subscription records for two cellular networks in 1996. [This register-based approach precludes selection bias to non-response as well as recall bias in the ascertainment of mobile phone use. Information on the frequency or duration of calls was not available, nor was mobile-phone use under a corporate account.]

A case–control study by Hardell *et al.* (2004) (Table 2.19) included 267 cases, considered both benign and malignant tumours of the parotid gland, and provided detailed exposure information. Again, the results were null. [The study included few people who had used mobile phones for > 10 years.]

A case–control study by Lönn *et al.* (2006) (Table 2.19), which was part of the INTERPHONE study, included 172 cases (benign and malignant parotid tumours combined), 681 controls (for the 60 malignant cases), and 321 controls (for the 112 benign cases). The study found no association with regular use of mobile phones for either malignant or benign parotid tumours. The surrogate exposure metrics considered included frequency of use, duration of regular use, time since first regular use, cumulative use and cumulative number of calls. For benign tumours, there was a slightly elevated risk associated with ipsilateral use of mobile phones (OR, 1.4; 95% CI, 0.2–2.2, based on 51 cases) but not for contralateral tumours (OR, 0.7; 95% CI, 0.4–1.1, based on 35 cases). [There may have been bias in reporting of laterality of phone use.]

A case–control study of tumours of the parotid gland was conducted in Israel, where use of mobile phones was reported to be very high (Sadetzki *et al.*, 2008; Table 2.19). This was the largest study of this type (402 cases with benign tumours, 58 with malignant tumours, and 1266 controls), also conducted as part of the INTERPHONE study. Cases were diagnosed at age 18 years or more during 2001 and 2003. In the main analyses, no increased risk was observed for any of the exposure surrogates examined. Laterality analyses generally indicated increased risk for ipsilateral use and reduced risk for contralateral use, e.g. for > 266 hours of cumulative call time with no hands-free devices, the odds ratio for ipsilateral use was 1.49 (95% CI, 1.05–2.13, based on 115 cases), while the odds ratio for contralateral use was 0.84 (95% CI, 0.55–1.28, based on 48 cases). Stratified analyses according to type of residence produced a somewhat higher odds ratio for rural and mixed rural/urban areas than for poor urban areas. For rural and rural/urban users, exposure–response associations were significant for cumulative call time (P = 0.04) and borderline significant for number of calls (P = 0.06). When the analyses were restricted to regular users only, taking the lowest category of use as the reference, increased odds ratios were found if time since start of use was > 5 years before diagnosis (OR, 1.40; 95% CI, 1.03–1.90, based on 134 cases) and for the highest exposure category of cumulative number of calls (OR, 1.51; 95% CI, 1.05–2.17, based on 81 cases) and duration of calls (OR, 1.50; 95% CI, 1.04–2.16, based on 83 cases). [The fact that there were increased odds ratios for ipsilateral tumours and decreased odds ratios for contralateral tumours suggested the presence of bias in reporting side of use.]

In a hospital-based case–control study of epithelial cancers of the parotid gland conducted in China between 1993 and 2010 (136 cases, 2051 controls), no overall association of cancer risk with regular use of mobile phones was observed (Duan *et al.*, 2011; Table 2.19). The authors also evaluated several more detailed exposure metrics and commented that several showed evidence of a dose–response relationship. [This interpretation was made uncertain by aspects of variation in the odds ratios. In several instances, there was no indication of a gradient in risk, but a very large increase in the odds ratio for the highest exposure category. Perhaps more puzzling was the fact that, for many of the exposure variables, odds ratios for all categories of exposure were higher than the overall odds ratio of 1.14. One would expect the overall odds ratio for regular use to be a weighted average of category-specific odds ratios. For number of calls since first use, the authors reported an odds ratio of 15.36 (95% CI, 13.34–17.38) for the highest exposure category, based on one exposed case. This cannot be correct and raises doubt about other analyses. The odds ratio presented may be 1/OR, as 0.7% of cases and 12.6% of controls were in this category.]

The incidence of cancers of the salivary gland was not increased relative to that in the general population in a large cohort of mobile-phone subscribers in Denmark followed up for up to 21 years (Schüz *et al.*, 2006c; Table 2.19).

A recent descriptive study reported an increase in the occurrence of cancer of the parotid gland (not incidence rate) in Israel, which appeared to begin around 1990 and continue through 2006 (Czerninski *et al.*, 2011). [Interpretation of these findings was difficult given the increase in population size in Israel, possible improvements over time in the ascertainment of cancers of the parotid gland, a substantial shift in diagnoses over time from the category "major salivary gland cancers, not otherwise specified" to more precisely defined types – the large majority of which were cancers of the parotid gland – and the lack of information about mobile-phone use.]

2.3.6 Other cancers

(a) Cancer of the breast

[There was little information concerning mobile-phone use and risk of breast cancer.] Breast cancer did not occur more often than expected based on incidence rates in the general population in a cohort of 65 542 Danish female mobile-phone subscribers followed from as early as 1982 until 1995 (Schüz *et al.*, 2006c; Table 2.18).

(b) Cancer of the skin

In a case–control study of cutaneous melanoma in the head and neck region (347 cases, 1184 controls), Hardell *et al.* (2011b) reported no overall association with use of mobile phones (OR, 1.0; 95% CI, 0.7–1.3, based on 223 cases) or cordless phones (OR, 0.9; 95% CI, 0.6–1.2, based on 138 cases), nor among those with heavier use. Use of cordless phones, but not mobile phones, was associated with an increased risk of melanoma in the temporal region, cheek, and ear for the group with 1–5 year latency among those with heavier use (OR, 2.1; 95% CI, 1.1–3.8 for > 365 cumulative hours, based on 21 cases). [The overall pattern in the data pointed more in the direction of no effect. The odds ratio mentioned in the Abstract for the latency period of 1–5 years did not match that in Table 2 of the published manuscript regarding mobile-phone use.]

[To date, there have been no studies of non-melanoma skin cancer in relation to mobile-phone use.]

(c) Other cancer sites

Subscribers to mobile-phone services in Denmark followed from as early as 1982 until 2002 did not show significantly elevated incidence rates of cancers of the lung, larynx, bladder, buccal cavity, oesophagus, liver, uterine cervix, stomach, kidney, pancreas, prostate or other sites, relative to the incidence rates in the Danish general population (Schüz *et al.*, 2006c).

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3. CANCER IN EXPERIMENTAL ANIMALS

3.1 Studies of carcinogenicity

See Table 3.1

3.1.1 Mouse

Groups of 50 male and 50 female $B6C3F_1$ mice (age, 8–9 weeks) were sham-exposed or received whole-body exposure to GSM (Global System for Mobile communications)-modulated radiofrequency (RF) radiation at 902 MHz, or to DCS (Digital Cellular System)-modulated RF radiation at 1747 MHz, in a Ferris wheel/tube-restrained design for 2 hours per day, 5 days per week, for 24 months. Exposures were performed with a three-phase signal imitating "basic," "talk" and "environment" GSM signals. Cage controls were run in parallel. The average specific absorption rate (SAR) for each signal phase (0, 0.4, 1.3, and 4.0 mW/g), organ-averaged SARs, and corresponding standard variations were calculated. No increases in tumour incidence at any site were observed in exposed mice compared with sham-exposed mice. Decreases in the incidence of liver adenoma were seen in males exposed to GSM at 4.0 mW/g and in males exposed to DCS at 4.0 mW/g (Tillmann *et al.*, 2007).

3.1.2 Rat

Groups of 100 male Sprague-Dawley rats (age, 8 weeks) were sham-exposed or exposed to RF radiation as pulsed microwaves at 2450 MHz, at 800 pulses per second (pps) with a pulse width of 10 μs (range of SAR values: young rats, 0.4 mW/g; older rats, 0.15 mW/g) for 21.5 hours per day, 7 days per week, for 25 months. The exposure to microwaves had no statistically significant effect on survival (median survival time: sham-exposed rats, 663 days; exposed rats, 688 days) or body weight. No statistically significant increases in the incidence of any benign or malignant tumours were identified at any site in exposed rats compared with sham-exposed controls. An increased incidence of total malignant tumours (all sites) was observed in rats exposed to RF radiation compared with sham-exposed controls (Chou *et al.*, 1992). [The Working Group considered this finding to be of limited biological significance, since it resulted from pooling of non-significant changes in tumour incidence in several sites.]

Groups of female Sprague-Dawley rats (age, 52–70 days) were sham-exposed or exposed to RF radiation as GSM at 900 MHz, with a pulse of 217 Hz, for more than 23 hours per day, 7 days per week, for up to 37 months. In the four experiments that were carried out, the number of rats per group was 12 in experiments 1 and 2, and 30 in experiments 3 and 4. Rats were group-housed with up to 12 rats per cage. Whole-body averaged SARs (wbSARs) during the studies ranged from 32.5–130 mW/kg in rats weighing 170–200 g, to 15–60 mW/kg in rats weighing ~400 g. In experiment 1, surviving rats were killed and necropsied at 770 days [26.7 months] (mortality, 33%), while in experiment 2, surviving rats were killed and

Table 3.1 Studies of carcinogenicity in experimental animals exposed to radiofrequency radiation

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours			Significance	Comments
Mouse, C3H/HeA (F) 10.5 mo Szmigielski et al. (1982)	2 450 MHz MW far field: sham, 5 mW/cm^2 (SAR, 2–3 mW/g), 15 mW/cm^2 (SAR, 6–8 mW/g), confinement stress group, cage control 2 h/d, 6 d/wk 40/group	Power density (mW/cm^2)	Mammary-gland tumours	CDT_{50}	*P < 0.01	Mammary-gland tumours detected only by palpation
			at 8 mo / at 10 mo			
		0 (sham)	3/40 / 14/40	322 d		
		5	18/40* / 32/40*	261 d		
		15	26/40* / 37/40*	219 d		
		Confined	16/40* / 31/40*	255 d		
Mouse, *Eμ-Pim1* (F) 18 mo Repacholi et al. (1997)	900 MHz (217 Hz [pulse repetition, similar to GSM]; pulse width, 0.6 ms), sham SAR: 0.008–4.2 mW/g, 0.13–1.4 mW/g (average) 2 × 30 min/d, 7 d/wk 100/sham-exposed group, 101/RF radiation-exposed group	Lymphoma (sham, RF-EMF): 3/100, 6/101 (lymphoblastic) 19/100, 37/101 (non-lymphoblastic) 22/100, 43/101 (all)			P = 0.0002 (non-lymphoblastic lymphoma) P = 0.006 (all lymphomas)	No standardized assessment criteria were defined for deciding which mice would be selected for necropsy. Mice surviving the 18 mo of exposure or sham-exposure were discarded without necropsy.
Mouse, C3H/HeJ (F) 21 mo Toler et al. (1997)	435 MHz (420–450 MHz) RF radiation with pulse-wave (pulse width, 1.0 μs; pulse rate, 1.0 kHz), sham Incident power density of 1.0 mW/cm^2; SAR, 0.32 mW/g 22 h/d, 7 d/wk 200/group	Mammary-gland adenocarcinoma: 77/193 (exposed), 74/190 (sham)			NS	Complete histopathology
Mouse, C3H/HeJ (F) 18 mo Frei et al. (1998a)	2 450 MHz MW (SAR, 0.3 mW/g), sham 20 h/d, 7 d/wk 100/group	Mammary-gland carcinoma: 44% (RF radiation), 52% (sham)			NS	Complete histopathology
Mouse, C3H/HeJ (F) 78 wk Frei et al. (1998b)	2 450-MHz MW (SAR: 1.0 mW/g), sham 20 h/d, 7 d/wk 100/group	Mammary-gland carcinoma: 38% (RF radiation), 30% (sham)			NS	Complete histopathology

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeJ (F) 76 wk Jauchem et al. (2001)	UWB (rise time, 176 ps; fall time, 3.5 ns; pulse width, 1.9 ns; peak energy field, 40 kV/m; repetition rate, 1 kHz; SAR, 0.0098 mW/g), sham 2 min/wk, 12 wk 100/group	Mammary-gland carcinoma: 48/100 (UWB), 52/100 (sham)	NS	Complete histopathology
Mouse, *Eμ-Pim1* and wild-type (C57BL/6NTac) (F) 104 wk Utteridge et al. (2002)	GSM-modulated 898.4 MHz (pulse width, 0.6 ms); SAR, 0.25, 1.0, 2.0, 4.0 mW/g; sham, cage control 1 h/d, 5 d/wk 120/group (wild-type and *Eμ-Pim1*)	Number of tumour-bearing animals: *Lymphoblastic lymphoma* Sham-exposed control (wild-type, transgenic): 3, 15; SAR = 0.25: 0, 8*; SAR = 1: 2, 8; SAR = 2: 2, 9; SAR = 4: 0, 15; total: 7, 55 *Non-lymphoblastic lymphoma* Sham-exposed control (wild-type, transgenic): 35, 74; SAR = 0.25: 40, 80; SAR = 1: 35, 78; SAR = 2: 43, 84; SAR = 4: 36, 84; total: 189, 400 *Neurological tumours* Sham-exposed control (wild-type, transgenic): 11, 1; SAR = 0.25: 17, 4; SAR = 1: 15, 0; SAR = 2: 10, 2; SAR = 4: 9, 2; total: 62, 9	*$P = 0.02$ (decrease)	Restrained exposure (Ferris wheel) also for sham, but cage-control group unrestrained. Necropsy was performed on all mice.
Mouse, AKR/J (F) 40 wk Sommer et al. (2004)	GSM 900 MHz (overall max. SAR, 5.9 mW/g; average SAR, 0.4 mW/g [whole body]), sham 24 h/d, 7 d/ wk 160/group	No increase in tumour incidence	NS	Histopathology was performed on spleen, thymus, lymph nodes, liver, kidney, lung and brain.
Mouse, *Eμ-Pim1* (M, F) 18 mo Oberto et al. (2007)	GSM-modulated 900 MHz (pulse width, 0.577 ms); SAR, 0.5, 1.4, 4.0 mW/g (whole body); sham, cage control 2 × 30 min/d, 7 d/wk 50 M and 50 F/group	Number of tumour-bearing animals: *Lymphoma* (all): (M) – 8 (cage), 9 (sham), 10 (0.5, 1.4 mW/g), 3 (4 mW/g); (F) – 26 (cage), 22 (sham), 18 (0.5 mW/g), 30 (1.4 mW/g), 20 (4.0 mW/g) *Harderian gland adenoma*: (M) – 0 (sham), 0 (0.5 mW/g), 2 (1.4 mW/g), 4 (4.0 mW/g)	Harderian-gland adenoma: $P = 0.0028$ (one-tailed test, trend) (M)	Restrained exposure (Ferris wheel). Mortality was higher ($P < 0.05$) in all three groups of exposed males and in the females exposed at 0.5 mW/g. GLP

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 24 mo Tillmann et al. (2007)	GSM 902 MHz, DCS 1 747 MHz, sham, cage control; wbSAR: 0.4, 1.3, 4 mW/g for each signal. 2 h/d, 5 d/wk 50 M and 50 F/group	*All tumours* (%) GSM (M/F):sham (68/78), low dose (62/78), medium dose (66/74), high dose (64/78); DCS (M/F): sham (74/74), low dose (60/62), medium dose (50/70), high dose (48/66) DCS: No. of males with tumours: 37 (sham), 30 (low dose), 25 (medium dose)* and 24 (high dose)*; No. of males with benign tumours: 27 (sham), 21 (low dose), 17 (medium dose), 12 (high dose)* *Liver adenoma in males* (%) DCS: 22 (sham), 4 (high dose)*; GSM: 30 (sham); 12 (high dose)*	*$P < 0.05$ (decrease)	Restrained exposure (Ferris wheel) Complete histopathology GLP
Mouse, *Ptc1*$^{+/-}$, *Ptc1*$^{+/+}$ (wild-type) (M, F) Lifetime Saran et al. (2007)	GSM-modulated 900 MHz (wbSAR, 0.4 mW/g), sham, cage control 2 × 30 min/d, 5 d, starting on PND 2 23–26 heterozygous and 22–29 wild-type mice/sex/group	No increase in tumour incidence	NS	Histopathology was performed on brain, a 5 cm^2 piece of skin, and any visible neoplasm.
Mouse, AKR/J (F) 43 wk Sommer et al. (2007)	UMTS (FDD, 1 966 MHz; SAR, 0.4 mW/g), sham, cage control 24 h/d, 7 d/wk 160/sham- or RF radiation-exposed group and 30/cage-control group	*Lymphoma* RF radiation: 141 (88.1%); sham: 149/150 (93.1%); cage control, 29/30 (96.7%)	NS	Histopathology was performed on spleen, thymus, lymph nodes, liver, kidney, lung and brain.
Mouse, AKR/J (M, F) 42 wk Lee et al. (2011)	CDMA 849 MHz and WCDMA 1950 MHz (combined) with SAR of 2 mW/g for CDMA and WCDMA [variation estimated: 1.59–2.52 mW/g], sham 45 min/d, 5 d/wk 40 M and 40 F/group	*Thymic lymphoma* Sham: M: 30/40 (75%); F: 32/40 (80%) Combined RF radiation: M: 31/40 (78%); F: 31/40 (78%)	NS	Exposure was performed in a reverberation chamber. Histopathology was performed on spleen, thymus, lymph nodes, liver, kidney, lung and brain.
Rat, Sprague-Dawley (M) 25 mo Chou et al. (1992)	2 450 MHz (800 pps; pulse width, 10 µs; pulse modulation, 8 Hz), sham; SAR: 0.15 (800 g bw) and 0.4 mW/g (200 g bw) 21.5 h/d, 7 d/wk 100/group	*Malignant neoplasms (all sites)* Sham, 5/100; exposed, 18/100 *Adrenal gland, pheochromocytoma* Sham, 1/100; exposed, 7/100 *Adrenal gland, cortical carcinoma* Sham, 0/100; exposed, 3/100	$P = 0.005$, χ^2 NS	Complete histopathology No increase in tumour incidence at any site.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 24 mo La Regina et al. (2003)	FDMA 835.6 MHz, CDMA 847.7 MHz, sham; SAR (brain): 0.85 ± 0.34 mW/g (time-averaged SAR), 1.3 ± 0.5 mW/g (nominal time-averaged brain SAR) 4 h/d, 5 d/wk 80 M and 80 F/group	*Total No. of tumours* (Sham/FDMA/CDMA): 76/79/78 (F), 163/162/148 (M) Mixed glioma (%): 0/1/0 (F) Astrocytoma (%): 0/0/1 (F), 0/1/0 (M) Granular cell tumour (%): 1/0/0 (F), 0/1/0 (M)	NS	Restrained exposure (Ferris wheel). Over the 2-yr time-course study, the brain SAR varied from 0.5 to 2.5 mW/g. Complete histopathology, 20–30 brain sections were examined per rat.
Rat, F344 (M, F) 24 mo Anderson et al. (2004)	1 620 MHz Dams and pups: far-field exposure from GD 19 until weaning (pups aged 23 days). Pups (age, 36 days): near-field exposure of ~2 yr. Brain SAR: 0.16 mW/g (fetuses, far field), 0.16 or 1.6 mW/g (offspring, near-field), sham, cage control. 2 h/d, 7 d/wk (far-field), 2 h/d, 5 d/wk (near field) 80–90 M and 80–90 F pups/group: near-field (2 groups), sham (1 group), cage control (1 group)	No increase in tumour incidence	NS	Restrained exposure (Ferris wheel) for near-field exposure Complete histopathology The incidence of brain neoplasms was within the range for historical controls
Rat, Wistar (M, F) 24 mo Smith et al. (2007)	902 MHz (GSM), 1 747 MHz (DCS), sham, cage control; time-averaged wbSAR: 0.44, 1.33, 4.0 mW/g for each signal. 2 h/d, 5 d/wk 50 M and 50 F/group	No increase in tumour incidence	NS	Restrained exposure (Ferris wheel) Due to increase in bw, the wbSAR of the group at the highest dose (4.0 mW/g targeted) was reduced to 3.0 mW/g after about 2 years; on average, a wbSAR of 3.7 mW/g was obtained; detailed SAR values and uncertainty were estimated for many organs. Complete histopathology GLP

bw, body weight; B[*a*]P, benzo[*a*]pyrene; CDMA, code-division multiple access; CDT_{50}, cancer-development time 50 (i.e. time in which 50% of the mice developed skin carcinoma); d, day; DCS, digital personal communications system; FDD, frequency-division duplexing; FDMA, frequency-division multiple access; GD, day of gestation; GLP, good laboratory practice; GSM, Global System for Mobile Communication; min, minute; mo, month; MW, microwave; NS, not significant; PND, postnatal day; RF-EMF, radiofrequency electromagnetic field; SAR, specific absorption rate; UWB, ultra-wide band; WCDMA, wide-band code division multiple access; wk, week; yr, year

necropsied at 580 days [19.3 months] (mortality, 50%). In experiment 1, histopathological evaluations were performed on the main organs, while only gross pathology was performed in experiment 2. In experiments 3 and 4, the rats were followed until natural death and histopathology was done on macroscopically detected changes only. In experiments 1 and 2, fewer pituitary tumours were detected in rats exposed to RF radiation (42% and 33% in experiments 1 and 2, respectively) than in sham-exposed controls (75% and 50% in experiments 1 and 2, respectively). Decreased incidences of mammary tumours (possibly associated with significantly shortened median survival times) were seen in experiments 3 and 4. No evidence of increased incidence of cancer in any tissue was reported in exposed rats compared with sham-exposed controls in any of the four experiments performed (Bartsch *et al.*, 2010). [The Working Group considered that the value of these experiments was limited by the lack of reproducibility in survival times in experiments 1 and 2 (performed with identical protocols), by the small group sizes in all experiments, and by the poor reporting of tumour data from all experiments. Because complete pathology results were not reported, this study cannot be regarded as a comprehensive carcinogenicity bioassay, and it was not considered in the evaluation.]

Groups of 80 female and 80 male F344 rats (age, 6 weeks) were sham-exposed or exposed to RF radiation in the FDMA mode (frequency-division multiple access) 835.6 MHz, or in the CDMA mode (code-division multiple access) at 847.7 MHz, for 4 hours per day, 5 days per week, for 24 months. Rats were tube-restrained during exposure; time-averaged SAR in the brain was 1.3 mW/g for both signals. There were no significant differences in survival, body weight or tumour incidence at any site in exposed males or females when compared with sex-matched sham-exposed controls (La Regina *et al.*, 2003).

Groups of pregnant Fischer 344 rats were exposed to far-field RF radiation at 1620 MHz for 2 hours per day, 7 days per week, from day 19 of gestation until weaning. At age 36 days, groups of 90 male and 90 female offspring were sham-exposed or exposed in tubes to near-field RF radiation at 1620 MHz (head mostly) for 2 hours per day, 5 days per week, for 24 months. Sham-exposure and near-field exposure were performed using a Ferris wheel/tube-restrained design at two targeted levels (brain SAR, 0.16 and 1.6 mW/g). No statistically significant differences between exposed and control groups were observed in number of live pups per litter, survival index, or weaning weights. There were no statistically significant effects of exposure on mean body weight of surviving rats. The percentage of rats surviving at study termination did not differ among groups. Incidences of tumours were similar in all groups (Anderson *et al.*, 2004).

Groups of 50 male and 50 female Wistar rats (age, approximately 6 weeks) were sham-exposed or received whole-body exposure to GSM-modulated RF radiation at 902 MHz, or to DCS-modulated RF radiation at 1747 MHz, in a Ferris wheel/tube-restrained design for 2 hours per day, 5 days per week, for 24 months. Exposures were performed with a three-phase signal imitating "basic," "talk" and "environment." Cage controls were run in parallel. Time-averaged wbSARs in the three exposure groups were 0.44, 1.33, and 4.0 mW/g for each signal phase. Body weight and survival were not statistically different between exposed and sham-exposed groups. No significant differences in the incidences of benign or malignant neoplasms at any site were observed between the exposed and sham-exposed groups (Smith *et al.*, 2007).

3.1.3 Transgenic and tumour-prone models

(a) Eμ-pim1 *transgenic mouse*

The *Eμ-Pim1* transgenic mouse strain has been reported to spontaneously develop lymphoma and to show an increased incidence of lymphoma

in response to exposure to chemical carcinogens (Breuer *et al.*, 1989; van Kreijl *et al.*, 1998).

Groups of 100–101 female heterozygous *Eμ-Pim1* mice (age, 6–8 weeks) were sham-exposed or exposed to RF radiation as "GSM basic" at 900 MHz for up to 18 months. Mean SAR values in exposed mice were 0.13–1.4 mW/g. At study termination, mice that were clinically healthy were counted as survivors and discarded without further investigation. Exposure to RF radiation had no statistically significant effect on body weight [survival data were not reported]. The authors reported a twofold increase in the incidence of lymphoma in *Eμ-Pim1* mice exposed to GSM RF radiation ($P = 0.006$ versus the sham-exposed group) (Repacholi *et al.*, 1997). [The Working Group considered the complete lack of pathology data to be a major limitation in the design of this study.]

Groups of 120 female heterozygous *Eμ-Pim1* mice and 120 female wild-type mice (C57BL/6NTac) (age, 7.5–9.5 weeks) were sham-exposed or exposed to GSM-modulated RF radiation at 898.4 MHz in a Ferris-wheel/restrained design at four different exposure levels (SAR: 0.25, 1.0, 2.0 or 4.0 mW/g) for 1 hour per day, 5 days per week, for 104 weeks. An unrestrained cage-control group was also included in the study. No significant differences in survival or body weight were observed between exposed and sham-exposed mice of either strain. Survival of the transgenic mice was significantly lower than that of wild-type mice ($P < 0.001$). No significant increases in the incidence of lymphoblastic or non-lymphoblastic lymphoma were seen in exposed mice compared with sham-exposed mice at any exposure level (Utteridge *et al.*, 2002).

Groups of 50 male and 50 female *Eμ-Pim1* mice (age, 9 weeks) were sham-exposed or exposed to RF radiation as "GSM basic" phase signal at 900 MHz, with a pulse of 217 Hz, and pulse width of 0.5 ms, at wbSARs of 0, 0.5, 1.4, or 4.0 mW/g. Exposures were for 1 hour per day, split into two sessions of 30 minutes (morning and afternoon), 7 days per week, for up to 18 months. Cage controls were run in parallel. As in the study by Utteridge *et al.* (2002), the mice were restrained in tubes during exposure or sham exposure. Compared with sham-exposed mice, survival until termination of the study was shorter in male mice in all groups exposed to RF radiation and in female mice exposed at 0.5 mW/g. Compared with sham-exposed groups, there was no significant difference in the mean body weight of either females or males. No statistically significant differences were seen in the incidences of malignant lymphoma (lymphoblastic and non-lymphoblastic) in sham-exposed or exposed males or females. The incidences of tumours of the Harderian gland were significantly higher in male mice exposed to RF radiation than in controls, with a dose-dependent trend ($P = 0.0028$, one-tailed test); this resulted in a significant positive trend in the overall incidence of benign tumours ($P < 0.01$). For females, no dose-related trends related to exposure to RF radiation were seen in the overall incidence of benign or malignant tumours, or of tumours regardless of type (Oberto *et al.*, 2007). [The Working Group noted that in the study of Repacholi *et al.* (1997), 22% of the sham-exposed female mice had lymphomas, whereas in this study, 44% of the sham-exposed and 52% of the cage-control female mice developed lymphomas. The incidence of lymphoma in the exposed group was 43% in the study of Repacholi *et al.* (1997), a value similar to that for the control groups in this study.]

(b) *Patched1$^{+/-}$ mouse*

Saran *et al.* (2007) used newborn *Patched1* heterozygous knockout mice (*Ptc1$^{+/-}$*), a mouse model characterized by predisposition to tumours of the brain and other tissues, and by hypersensitivity to ionizing radiation. Groups of 23–36 male and 23–36 female *Ptc1$^{+/-}$* mice, and groups of 22–29 male and 22–29 female wild-type mice were exposed to RF radiation at 900 MHz (wbSAR, 4 mW/g) from postnatal days 2 to

6 (30 minutes, twice per day), the time window of extreme susceptibility to induction of medulloblastoma by ionizing radiation in this strain. Mice were monitored throughout their lifespan for the onset of brain tumours or any other visible neoplasm. No significant differences between exposed and sham-exposed groups were observed in the incidence or size of medulloblastoma, or in the incidence of any other neoplasms in either *Ptc1*$^{+/-}$ mice or wild-type mice. [The Working Group noted that tumour data were not reported by sex. The very short duration of exposure, its timing during the immediate post-parturition period, and the lack of exposure of older juvenile or adult animals may limit the value of this study for hazard identification.]

(c) AKR mouse

The AKR mouse strain is known to develop lymphomas and other haematopoietic malignancies within the first year of life.

Groups of 160 unrestrained female AKR/J mice were sham-exposed or exposed to GSM-like RF radiation at 900 MHz for 24 hours per day, 7 days per week, for 40 weeks, at an average wbSAR of 0.4 mW/g. Exposure had a significant effect on body weight gain, with higher values in exposed than in sham-exposed mice. Survival and incidence of lymphoma did not differ between exposed and sham-exposed mice (Sommer *et al.*, 2004). [The Working Group noted that in the absence of any difference in survival, the ability of the study design to detect any effect on tumour incidence between groups was small.]

Groups of 160 female AKR/J mice (age, 8 weeks) were sham-exposed or exposed to RF radiation as Universal Mobile Telecommunications System (UMTS) at 1966 MHz (SAR, 0.4 mW/g) for 24 hours per day, for 248 days (43 weeks). The 30 mice in the cage-control group gained significantly less weight than did the exposed and sham-exposed animals. No statistically significant differences in total body weight, survival, or incidence of neoplasms were observed between exposed and sham-exposed mice. The incidence of lymphoma in all three groups was above 88% (RF-radiation exposed, 88.1%; sham-exposed, 93.1%; and cage controls, 96.7%) (Sommer *et al.*, 2007). [The Working Group noted that in the absence of any difference in survival, the ability of the study design to detect any effect on tumour incidence between groups was small.]

Groups of 40 female and 40 male AKR/J mice (age, 5 weeks) were exposed simultaneously to RF radiation at 849 MHz (SAR, 2 mW/g) and 1950 MHz (SAR, 2 mW/g), for 45 minutes per day, 5 days per week, for 42 weeks. Sham exposures were performed in parallel. No differences in body weight, survival or tumour incidence were observed. The incidence of lymphomas in all groups was greater than 75% (Lee *et al.*, 2011). [The Working Group noted the short daily exposure period. Furthermore, in the absence of any difference in survival, the ability of the study design to detect any effect on tumour incidence between groups was small.]

(d) C3H mouse

The C3H tumour-prone mouse carries a milk-borne virus that induces tumours of the mammary gland.

Groups of 40 female C3H/HeA mice were exposed to RF radiation at 2450 MHz as continuous microwaves from ages 6 weeks to 12 months. Five experimental groups (SAR, 0 [sham-exposed control], 2–3 mW/g, or 6–8 mW/g, confinement-stress group, cage-control group) were used. Mammary-gland tumours were detected by palpation. A more rapid appearance of mammary-gland tumours and a statistically significant increase in the incidence of mammary-gland tumours in both groups of mice exposed to microwave radiation was reported, compared with controls (Szmigielski *et al.*, 1982). [The Working Group noted that no histopathology was performed.]

Groups of 200 female C3H/HeJ mice were sham-exposed or received whole-body exposure

to a horizontally polarized pulse wave at 435 MHz (pulse width, 1.0 ps; pulse rate, 1.0 kHz; wbSAR, 0.32 mW/g) for 22 hours per day, 7 days per week, for 21 months. No statistically significant differences in survival or body weight, or in the incidence, latency or growth rate of mammary-gland tumours were seen between exposed and sham-exposed groups (Toler *et al.*, 1997).

Groups of 100 female C3H/HeJ mice (age, 3–4 weeks) were sham-exposed or exposed to continuous microwave radiation at 2450 MHz for 20 hours per day, 7 days per week, for 18 months. The average wbSAR was 0.3 mW/g. No significant differences in survival or body weight, or in the incidence, latency or growth rate of mammary-gland tumours were seen (Frei *et al.*, 1998a).

A study with a similar design was performed at a higher SAR (1.0 mW/g). Groups of 100 female C3H/HeJ mice (age, 3–4 weeks) were sham-exposed or exposed to continuous microwave radiation at 2450 MHz, for 20 hours per day, 7 days per week, for 78 weeks. No differences in survival or body weight or in the incidence, latency or growth rate of mammary-gland tumours were observed (Frei *et al.*, 1998b).

Groups of 100 female C3H/HeJ mice (age, 3–4 weeks) were exposed to pulses composed of an ultra-wide band (UWB) of frequencies with a rise time of 176 ps and a peak-energy field of 40 kV/m (SAR, 0.0098 mW/g). The mice were exposed for 2 minutes per week for 12 weeks, followed by a post-exposure period of 64 weeks. No significant differences between groups with respect to body weight, incidence of palpated mammary-gland tumours, latency to onset of mammary-gland tumour development, rate of mammary-gland tumour growth, or survival were found. Histopathological evaluations revealed no significant differences in tumour incidences between the two groups for all tissues studied (Jauchem *et al.*, 2001). [The Working Group considered that the exposure was very limited.]

(e) OF1 mouse

The Ico:OF1 mouse strain is known to develop spontaneous tumours of the lymphoid tissue. Groups of 20 female mice were sham-exposed or exposed to RF radiation at 800 MHz for 1 hour per week, for 4 months, and followed for up to 18 months (Anghileri *et al.*, 2005). Compared with controls, the exposure caused an earlier onset of general lymphocyte infiltration, formation of lymphoblastic ascites, and development of extranodal tumours of different histological types. [The Working Group considered that the inadequate description of the exposure level and dosimetry, the lack of histopathology, and the small group size did not permit a proper evaluation of this study.]

3.2 Initiation–promotion studies

See Table 3.2

The effect of exposure to RF radiation on tumours initiated by a chemical or physical carcinogen has been tested in various rodent models.

3.2.1 Skin-tumour model

Four groups of female ICR mice (age, 10 weeks) were given a single application of 100 µg of 7,12-dimethylbenz[*a*]anthracene (DMBA) on pre-shaved dorsal skin. Exposure to RF radiation started 1 week later and was continued for 19 weeks. Group 1 (48 mice) was exposed to a TDMA (time-division multiple access) signal at 1.49 GHz (50 pps, near-field), for 90 minutes per day, 5 days per week, at a skin local peak SAR of 2.0 mW/g. Group 2 (48 mice) was sham-exposed. Group 3 (30 mice) was exposed weekly and topically to 4.0 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) per mouse. Group 4 (30 mice) received no further treatment. The incidences of skin papilloma or carcinoma (combined) were 0 out of 48, 0 out of 48, 29 out of 30, and 1 out of 30, respectively (Imaida *et al.*, 2001).

In a comparable experiment, groups of 20 male ICR mice (age, 7 weeks) received the same single skin application (100 μg of DMBA per mouse). Exposure to RF radiation started 1 week later and was continued for 19 weeks. Group 1 was exposed topically to 4 μg of TPA per mouse, twice per week. Group 2 was sham-exposed. Group 3 was exposed to RF radiation at 849 MHz (45 minutes, twice per day, with an interval of 15 minutes between exposures, for 5 days per week). Group 4 was exposed to RF radiation at 1763 MHz (with a schedule similar to that for group 3). A CDMA signal was used with a wbSAR of 0.4 mW/g. Skin tumours [not further specified] were detected only in the DMBA/TPA-treated positive control group (Huang *et al.*, 2005). [The Working Group noted the short duration of daily exposures and the use of only one exposure level per experiment.]

Groups of 10 male Swiss albino mice (age, 8 weeks) received a single skin application of 100 μg of DMBA (initiated groups) or were left untreated. Exposure to RF radiation or to croton oil (the positive control) started 2 weeks later. Group 1 was not initiated and was sham-exposed. Group 2 was exposed to DMBA only (cage control). Group 3 was exposed to DMBA plus amplitude-modulated (AM) RF radiation at 112 MHz, with a SAR of 0.75 mW/g, for 2 hours per day, 3 days per week, for 16 weeks. Group 4 was exposed to DMBA plus RF radiation at 2450 MHz with a SAR of 0.1 mW/g for 2 hours per day, 3 days per week, for 16 weeks. Group 5 was exposed to AM RF radiation at 112 MHz only. Group 6 was exposed to RF radiation at 2450 MHz only. Group 7 was exposed to DMBA plus a topical application of croton oil at 1% in 100 μL of acetone per mouse, twice per week, for 16 weeks. At study termination, skin tumours were detected only in the positive-control group (DMBA plus croton oil) (Paulraj & Behari, 2011). [The Working Group noted that the study was limited by the small group size and the relatively short duration of exposure.]

The promoting activity of RF radiation at 94 GHz was tested in groups of 27–55 female SENCAR mice previously initiated by dorsal application of DMBA at 10 nmol (2.56 μg). In a first experiment, 2 weeks after initiation, restrained mice were dorsally exposed once for 10 seconds to RF-EMF as follows: group 1 was exposed to millimetre wavelength (MMW) continuous wave far-field RF radiation (94 GHz, 1.0 W/cm^2) and group 2 was exposed to infrared radiation at 1.5 W/cm^2. Both exposures led to similar skin heating (13–15 °C). Mice in group 3 were sham-exposed. In the positive-control group, initiated mice received the promoter TPA. After 23 weeks, the incidence and multiplicity of skin tumours was found to be similar in mice exposed to RF radiation, infrared radiation or sham-irradiated. TPA significantly increased both incidence and multiplicity of skin tumours compared with the other groups. [The Working Group noted that the importance of these findings was diminished by the very limited exposure to RF radiation.] In a second experiment, the effects of repeated exposure to RF radiation (333 mW/cm^2) or infrared radiation (600 mW/cm^2) for 10 seconds, twice per week, for 12 weeks, on skin-cancer promotion or co-promotion together with TPA were investigated. Groups of 50 female SENCAR mice were initiated with DMBA as above, and promotion treatment was started 2 weeks later. Group 1 was exposed to DMBA and sham-exposed; group 2 was exposed to DMBA + TPA and sham-exposed; group 3 was not initiated, exposed to TPA, and sham-exposed; group 4 was exposed to DMBA plus RF radiation at 333 mW/cm^2; group 5 was exposed to DMBA plus RF radiation at 333 mW/cm^2 plus TPA; group 6 was exposed to DMBA plus infrared radiation at 600 mW/cm^2; group 7 was exposed to DMBA plus infrared radiation at 600 mW/cm^2 plus TPA; and group 8 was sham-exposed only. The study was terminated 25 weeks after initiation. TPA promotion increased the incidence and multiplicity of skin tumours. Exposure to RF or infrared radiation did not

Table 3.2 Initiation–promotion studies in experimental animals exposed to radiofrequency radiation

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, CBA/S (F) X-ray ionizing radiation, 4–6 MV (4 Gy as three 1.33 Gy fractions at 1-wk intervals) on wk 1 78 wk Heikkinen et al. (2001)	902.5 MHz (continuous NMT900), SAR, 1.5 mW/g; 902.4 MHz (pulsed GSM, 217 Hz), SAR, 0.35 mW/g; sham; and cage controls Time averaged input power: 6.1 ± 0.8 W for continuous RF group and 1.3 ± 0.1 W for pulsed RF group 1.5 h/d, 5 d/wk, 78 wk 50/group	Lymphoma (cage, sham, NMT and GSM): 0/50, 12/50, 12/50, 10/50	NS	Restrained exposure Full histopathology
Mouse, ICR (F) DMBA (dermal): 100 µg/100 µL acetone/mouse on wk 1 20 wk Imaida et al. (2001)	1.49 GHz TDMA signal (50 pulses/s), near-field 90 min/d, 5 d/wk, 19 wk (on wk 2) SAR (skin): 2.0 mW/g, SAR (wb, av): 0.084 mW/g	Skin squamous cell papilloma or carcinoma (combined), tumour multiplicity		
	Group 1: DMBA + RF-EMF (n = 48)	0/48, 0	NS	
	Group 2: DMBA + sham (n = 48)	0/48, 0	NS	
	Group 3: DMBA + TPA (n = 30)	29/30*, 18.8 ± 13.4*	*$P < 0.001$	
	Group 4: DMBA + cage control (n = 30)	1/30, 0.1 ± 0.5	-	
Mouse, SENCAR (F) DMBA (dermal): 10 nmol/200 µL acetone on wk 1 *Exp. 1* and *Exp. 2*: 25 wk Mason et al. (2001)	*Exp. 1:* 94 GHz MMW CW far-field or IR heating, single skin exposure of 10 s (on wk 3); TPA, 2 × /wk for 23 wk	*Exp. 1:* Comparable skin tumour incidence and multiplicity in sham-, MMW- or IR-exposed groups. TPA increased incidence and multiplicity of skin tumours.		No SAR given
	Group 1: DMBA + 1.0 W/cm² MMW (n = 55)			
	Group 2: DMBA + 1.5 W/cm² IR for 10 s (n = 55)			
	Group 3: DMBA + sham (n = 55)			
	Group 4: DMBA + TPA (n = 27)			
	Exp 2: MMW or IR, skin exposure of 10 s, 2 × /wk, 12 wk; TPA, 2 × /wk for 23 wk	*Exp. 2:* TPA promotion led to increased incidence and multiplicity of DMBA-induced skin tumours; exposure to MMW or IR did not further increase the incidence or multiplicity of DMBA + sham or DMBA + TPA + sham-induced skin tumours.		
	Group 1: DMBA + sham			
	Group 2: DMBA + sham + TPA			
	Group 3: sham + TPA			
	Group 4: DMBA + 333 mW/cm² MMW			
	Group 5: DMBA + MMW + TPA			
	Group 6: DMBA + 600 mW/cm² IR			
	Group 7: DMBA + IR + TPA			
	Group 8: sham			
	50/group			

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours		Significance	Comments
Mouse, ICR (M) DMBA (dermal): 100 µg/100 µL acetone/mouse on wk 1 20 wk Huang et al. (2005)	849 MHz CMDA signal or 1 763 MHz CMDA signal 2 × 45 min/d (15-minute interval between exposures), 5 d/wk, 19 wk (on wk 2) SAR (wb, av): 0.4 mW/g Group 1: DMBA + TPA Group 2: DMBA + sham Group 3: DMBA + 849 MHz Group 4: DMBA + 1 763 MHz 20/group	No skin tumours in RF-EMF-exposed groups. Skin tumours (95%) in DMBA + TPA group only.		NS	Free-moving mice were exposed in a reverberation chamber. The short duration of daily RF-EMF-exposure is questionable.
Mouse, Swiss (M) DMBA (dermal): 100 µg on wk 1 18 wk Paulraj & Behari (2011)	112 MHz, AM at 16 Hz (1.0 mW/cm^2; SAR, 0.75 mW/g) or 2 450 MHz (0.34 mW/cm^2; SAR, 0.1 mW/g) 2 h/d, 3 d/wk, 16 wk (on wk 3) Group 1: control Group 2: DMBA Group 3: DMBA + 112 MHz Group 4: DMBA + 2 450 MHz Group 5: 112 MHz Group 6: 2 450 MHz Group 7: DMBA + croton oil 18/group	No skin tumours in any group, except in group 7			Small group size and short duration of exposure
Rat, F344 (M, F) ENU *in utero*, 4 mg/kg bw iv on GD 18 24 mo Adey et al. (1999)	836.55 MHz, NADC-modulated Far-field: GD 19–PND 21 (weaning) 2 h/d, 7 d/wk Near-field: starting on PND 33/35 2 h/d (8 × 7.5 min field on/off), 4 d/wk, 22 months SAR (brain): 1.1–1.6 mW/g SAR (wb, av): 1.8–2.3 mW/g				Ferris wheel/restrained exposure 25 (M) or 20 (F) sections per brain
		CNS tumours			
		Total [%]	Brain [%]		
	Group 1: sham/sham, *n* = 30 M + 30 F	11.7	8.3	-	
	Group 2: sham/RF, *n* = 30 M + 30 F	3.3	3.3	NS	
	Group 3: ENU/sham, *n* = 30 M + 30 F	16.7	15.0	-	
	Group 4: ENU/RF, *n* = 30 M + 26 F	7.1	3.6	NS	

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (F) B[*a*]P, 2 mg s.c. 160 d Chagnaud et al. (1999)	900 MHz, GSM-modulated, far-field (55 or 200 μW/cm²) SAR (wb, av): 75 or 270 mW/kg Exposure started on d 20, 40 or 75 after B[*a*]P initiation 2 h/d, 5 d/wk, 2 wk	Small palpable tumours (sarcomas) detectable from d 90–100 onwards. Tumour incidence not reported. No consistent pattern of differences in time to tumour or survival.	NS	Poor and confusing description of experiment and results. The authors stated that tumour onset was "slightly different" ($P = 0.05$) in the sham-exposed group and one of the exposed groups (55 μW/cm², 40 days).
Rat, F344 (M, F) ENU *in utero*, 4 mg/kg bw i.v. on GD 18 24 mo Adey et al. (2000)	836.55 MHz, NADC-modulated Far-field: GD 19–PND 21 (weaning) 2.6 ± 0.50 mW/cm² Near-field: PND 31–731/734 2 h/d (8 × 7.5 min field on/off), 4 d/wk SAR (brain): 1.1–1.6 mW/g SAR (wb, av): 1.8–2.3 mW/g	Primary CNS tumours		Ferris wheel/restrained exposure 25 (M) or 20 (F) sections per brain

Group	RF (μW/cm²)	No. of rats (sham/RF)	No. of days after B[*a*]P initiation
1, 2	55	17/17	20
3, 4	55	18/18	40
5, 6	55	14/17	75
7, 8	200	8/9	40
9	cage control	6	-

	Total [%]	Brain [%]	
Group 1: sham/sham, $n = 45$ M + 45 F	1.1	1.1	-
Group 2: sham/RF, $n = 45$ M + 45 F	4.4	3.3	NS
Group 3: ENU/sham, $n = 45$ M + 45 F	22.2	18.9	-
Group 4: ENU/RF, $n = 38$ M + 52 F	17.8	15.6	NS
Group 5: ENU/cage control, $n = 45$ M + 45 F	14.4	14.4	
Group 6: cage control, $n = 45$ M + 45 F	4.4	3.3	

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) ENU *in utero*, on GD 15, 0, 2.5 or 10 mg/kg bw i.v. 24 mo Zook & Simmens (2001)	860 MHz, PW or CW, near-field 6 h/d, 5 d/wk, 22 months (starting on PND 57)	No evidence that PW or CW increased the incidence of tumours in any studied tissues or promoted cranial or spinal or spinal nerve-cord tumours initiated by ENU.	NS (overall)	Restrained exposure of the head in tube (Ferris wheel) GLP Tissues studied histologically included brain (18–26 step sections [1 mm]/brain), spinal cord, trigeminal nerves, lungs, liver, heart, kidneys, spleen, adrenal, pituitary and thyroid glands, and any gross lesions, including all neoplasms.
	SAR (brain, av): 1.0 ± 0.2 mW/g			
	SAR (wb, av): 0.27–0.42 mW/g			
	15 groups, 30 M + 30 F/group	No. of rats with brain tumours (M + F combined)		

Group	ENU (mg/kg bw)	RF	All	Multiple	Astrocytoma	Oligodendroglioma	Mixed glioma	
1	0	PW	5	0	5	0	0	NS
2	0	Sham	3	0	3	0	0	-
9	0	CW	3	0	2	1	0	NS
10	0	Sham	5	0	5	0	0	-
13	0	Cage control	6	0	5	1	0	
5	2.5	PW	7	2	4	2	4	NS
6	2.5	Sham	9	1	3	2	5	-
7	2.5	CW	9	0	2	6	1	NS
8	2.5	Sham	10	1	5	5	1	-
11	2.5	CW	3	0	0	0	3	NS
12	2.5	Sham	6	0	3	1	3	-
14	2.5	Cage control	5	0	0	4	0	
3	10.0	PW	36	15	0	26	32	NS
4	10.0	Sham	35	12	3	19	26	-
15	10.0	Cage control	41	9	2	24	25	

Rat, Sprague-Dawley (F) DMBA, 50 mg/kg bw by gavage 259–334 d Bartsch et al. (2002)	900 MHz GSM signal (217 Hz pulsed; pulse width, 577 µs) Far-field, 100 µW/cm² ± 3 dB; SAR (wb, av), 17.5–70 mW/kg 23 h/d, 7 d/wk Two groups each in three similar experiments performed over 3 years, 60/group	Mammary-gland tumours							Malignant tumours were adenocarcinomas
		Median tumour latency (d)		Cumulative incidence of tumours Last day of observation	[%]				
		Malignant	Benign		Malignant	Benign	Malignant	Benign	
	Exp. 1: Sham	145	316	334	79	90	-	-	
	Exp. 1: Exposed	278	310	334	82	91	$P = 0.009$ (retardation)	NS	
	Exp. 2: Sham	95	> 265	259	84	38	-	-	
	Exp. 2: Exposed	95	221	259	94	60	NS	NS	
	Exp. 3: Sham	216	293	343	91	89	-	-	
	Exp. 3: Exposed	195	321	343	81	92	NS	NS	

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours					Significance	Comments
Rat, Sprague-Dawley (M, F) ENU *in utero*, on GD 15, at 6.25 or 10 mg/kg bw i.v. Up to 24 months Zook & Simmens (2002, 2006)	860 MHz PW signal (frame rate, 11.1Hz; slot duration, 15-ms), near-field 6 h/d, 5 d/wk, up to 22 months (starting on PND 52) SAR (brain, av): 1.0 ± 0.2 mW/g SAR (wb, av): 0.27–0.42 mW/g 6 groups, 90 M + 90 F/group Group 1: ENU at 6.25 mg/kg bw + sham Group 2: ENU at 6.25 mg/kg bw + PW Group 3: 6.25 mg/kg bw ENU + cage control Group 4: 10.0 mg/kg bw ENU + sham Group 5: 10.0 mg/kg bw ENU + PW Group 6: 10.0 mg/kg bw ENU + cage control	Neurogenic tumours: PW does not affect incidence, multiplicity or latency. Brain tumours (No. of tumour-bearing rats) [6.25 and 10.0 mg/kg bw ENU-treated groups combined, M + F combined]:						Restrained exposure of the rat head in tube (Ferris wheel) GLP Study conducted in three phases. Each group included three cohorts of 30 M + 30 F. Euthanasia with 30-days intervals started on PND 171. Tissues that were studied histologically included brain (1-mm step sections), spinal cord, thyroid, pituitary and adrenal glands, liver, kidneys, lungs, spleen, heart, trigeminal nerves and any other tissues that appeared abnormal. The incidence, volume and malignancy grade of neurogenic tumours were increased in the group given ENU at 10 mg/kg bw compared with the group given ENU at 6.25 mg/kg bw. The incidences of tumours outside the nervous system were not associated with ENU treatment and were not increased in PW-exposed rats.
			All	*Multiple*	*Astrocytoma*	*Oligodendroglioma*	*Mixed glioma*		
	PW (360 animals at start)		173	61	1	111	100	NS	
	Sham (360 animals at start)		193	76	5	118	113	-	
	Cage control (360 animals at start)		180	58	6	106	107	-	
Rat, Sprague-Dawley (F) DMBA, 10 mg/rat by gavage on d 1 10 d + 9 wk (RF exposure) + 3 wk Anane et al. (2003)	900 MHz, GSM, far-field *Exp. 1*: SAR (wb, av): 0 (sham), 1.4, 2.2, 3.5 mW/g *Exp. 2*: SAR (wb, av): 0 (sham), 0.1, 0.7, 1.4 mW/g 2 h/d, 5 d/wk, 9 wk 16/group in both experiments	Mammary-gland tumours Rate of incidence of malignant tumours: *Exp. 1*: groups exposed at 1.4 and 2.2 mW/g *vs* sham *Exp. 2*: group exposed at 1.4 mW/g *vs* sham						$P = 0.02$, 0.04 (increase in rate of incidence) $P = 0.04$ (decrease in rate of incidence)	
		No. of tumours at wk 12				*No. of rats without tumour*	*No. of rats alive at wk 12*		
		Malignant		*Benign*					
	Exp. 1: Sham	21		5		5	16	-	
	1.4 mW/g	24		5		2	16	NS	
	2.2 mW/g	24		2		1	16	NS	
	3.5 mW/g	29		6		2	15	NS	
	Exp. 2: Sham	17		5		3	14	-	
	0.1 mW/g	8		11		0	14	NS	
	0.7 mW/g	13		15		4	16	NS	
	1.4 mW/g	4		4		9	16	NS	

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours				Significance	Comments
Rat, F344 (M, F) ENU *in utero*, 4 mg/kg bw i.v. on GD 18 24 mo Shirai et al. (2005)	1 439 MHz TDMA signal (near-field) 90 min/d, 5 d/wk, wk 5–109 (offspring) SAR (brain): 0.67, 2.0 mW/g SAR (wb, av): < 0.4 mW/g	Pituitary tumours lower in ENU/high group				$P < 0.01$	Tube exposure/restrained Full histopathology ~10 sections/brain
		CNS tumours [%]					
		Brain	Spinal cord				.
		M/F	M/F				
	Group 1: cage control	0/0	0/0				
	Group 2: ENU control	18/18	2/6				
	Group 3: ENU/sham	24/30	2/4			-	
	Group 4: ENU/low (0.67 mW/g)	30/18	0/6			NS	
	Group 5: ENU/high (2.0 mW/g)	22/16	4/4			NS	
	50 M + 50 F/group						
Rat, Sprague-Dawley (F) DMBA, 35 mg/kg bw by gavage on d 1 26 wk Yu et al. (2006)	900 MHz GSM; SAR (wb, av): 0.44, 1.33, 4.0 mW/g 4 h/d, 5 d/wk, 26 wk (starting on d 2)	No significant differences in incidence, latency, multiplicity or size of mammary-gland tumours between sham- and RF-exposed groups					
		Mammary-gland tumours (all) (%)	Mammary-gland adenocarcinoma (%)	Benign mammary-gland tumours (%)	Mammary-gland hyperplasia (%)		
	Group 1: cage control	60*	37	23*	14	*$P < 0.05$ *vs* sham	
	Group 2: sham	45	37	8	29		
	Group 3: 0.44 mW/g	38	25**	13	24	**$P = 0.058$ *vs* sham	
	Group 4: 1.33 mW/g	41	34	7	15		
	Group 5: 4.0 mW/g	43	38	5	24		
	99–100/group						
Rat, F344 (M, F) ENU *in utero*, 4 mg/kg bw i.v. on GD 18 24 mo Shirai et al. (2007)	1.95 GHz WCDMA signals for IMT-2000 cellular system (near-field) 90 min/d, 5 d/wk, wk 5–109 (offspring) SAR (brain): 0.67, 2.0 mW/g SAR (wb, av): ≤ 0.464 mW/g	Skin fibroma and large granular lymphocytic leukaemia incidences lower in ENU/high group				$P < 0.05$	Tube exposure/restrained Full histopathology ~10 sections/brain
		CNS tumours [%]					
		Brain	Spinal cord				
		M/F	M/F				
	Group 1: cage control	2/2	0/0				
	Group 2: ENU/cage control	16/14	2/0			-	
	Group 3: ENU/sham	8/10	2/0			NS	
	Group 4: ENU/low (0.67 mW/g)	16/10	0/0			NS	
	Group 5: ENU/high (2.0 mW/g)	16/22	2/0			NS	
	5 M + 50 F/group						

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours				Significance	Comments
Rat, Sprague-Dawley (F) DMBA, 17 mg/kg bw by gavage on d 1 6 mo Hruby et al. (2008)	902 MHz GSM (crest factor of 8; pulse width, 0.57 ms); SAR (wb, av), 0.4, 1.3, 4.0 mW/g 4 h/d, 5 d/wk, 6 mo (starting on d 2)					NS (RF-exposed *vs* sham-exposed)	Restrained exposure in tube (Ferris wheel) GLP Malignant tumours were mainly adenocarcinomas.
	100/group	Mammary-gland tumour multiplicity or volume					
		Mammary-gland lesions (%)					
		Malignant or benign	Malignant	Benign	Hyperplasia		
	Group 1: cage control	73	45	28	12		
	Group 2: sham	60	30	30	11		
	Group 3: 0.4 mW/g	57	40	17*	19	* $P < 0.05$ *vs* sham (decrease)	
	Group 4: 1.3 mW/g	50	35	15*	22		
	Group 5: 4.0 mW/g	65	47**	18*	9	** $P < 0.05$ *vs* sham (increase)	

B[*a*]P, benzo[*a*]pyrene; CDMA, code-division multiple access; CNS, central nervous system; CWRF, continuous-wave radiofrequency; d, day or days; DCS, Digital Personal Communication System; DEN, diethylnitrosamine; DMH, dimethylhydrazine; DMBA, 7,12-dimethylbenz[*a*]anthracene; EMF, electromoagnetic field; ENU, *N*-ethyl-*N*-nitrosourea; FDMA, frequency-division multiple access; GD, gestational day; GSM, Global System for Mobile communication; h, hour; i.v., intravenously; IR, infrared radiation; min, minute; MMW, millimetre wavelength; mo, month; NADC, North American Digital Cellular; NS, not significant; ODC, ornithine decarboxylase; PH, partial hepatectomy; PND, postnatal day; p.o., oral administration; PW, pulse-modulated radiofrequency; RF, radiofrequency radiation; s, second; SAR (wb, av), (time-averaged whole-body) specific absorption rate; s.c., subcutaneously; TDMA, time-division multiple access; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UMTS, Universal Mobile Telecommunication System; UWB, ultra-wide band; WCDMA, wide-band code-division multiple access; wk, week

increase tumour incidence or multiplicity when compared with DMBA-treated sham-exposed controls. Exposure to TPA and RF radiation or TPA and infrared radiation did not increase the incidence of tumours or tumour multiplicity when compared with TPA controls. The authors concluded that MMW did not promote or co-promote skin tumorigenesis (Mason *et al.*, 2001).

Starting at 20, 40, or 75 days after treatment with a single subcutaneous dose of 2 mg of benzo[*a*]pyrene, groups of 8–18 female Sprague-Dawley rats were exposed to GSM RF radiation at a wbSAR of 75 mW/kg for 2 hours per day, 5 days per week, for 2 weeks. An additional group was exposed to the GSM signal at a wbSAR of 270 mW/kg starting 40 days after the treatment with benzo[*a*]pyrene. For each GSM-exposed group, a sham-exposure group was included, resulting in a total of eight groups. The study was terminated at approximately 160 days after the treatment with benzo[*a*]pyrene. Small palpable tumours (sarcomas) were detectable from days 90 to 100. No consistent pattern of differences in time to tumour development or survival was observed between groups (Chagnaud *et al.*, 1999). [The Working Group noted that the value of this study was diminished by the very limited exposure, the small group sizes, and the absence of histopathology.]

3.2.2 Lymphoma model

CBA/S mice are prone to develop lymphomas after exposure to ionizing radiation. In this study, groups of 50 female CBA/S mice (age, 3–5 weeks) (except the cage-control group) received whole-body exposure to ionizing radiation (X-rays, 4–6 MV, 4 Gy, delivered as three equal fractions of 1.33 Gy at intervals of 1 week) at the beginning of the study, followed by exposure to RF radiation for 1.5 hours per day, 5 days per week, for 78 weeks. A first "X-ray plus RF" group was exposed to continuous NMT900 (Nordic Mobile Telephony 900)-type frequency-modulated RF radiation at a frequency of 902.5 MHz and a nominal average SAR of 1.5 mW/g. A second "X-ray plus RF" group was exposed to pulsed GSM-type RF radiation (carrier-wave frequency, 902.4 MHz; pulse frequency, 217 Hz) at a nominal average SAR of 0.35 mW/g. An X-ray-exposed control group received sham exposure to RF radiation. Exposure to RF radiation did not significantly increase the incidence of tumours compared with the sham-exposed group (Heikkinen *et al.*, 2001).

3.2.3 Mammary-gland tumour model

Groups of 60 female Sprague-Dawley rats (Hsd:SD) (age, 51 days) were given DMBA as a single intragastric dose of 50 mg/kg bw. On the same day, the rats were sham-exposed or exposed to RF radiation as a GSM signal at 900 MHz (pulse, 217 Hz) for 23 hours per day, 7 days per week, for 259–334 days. Over 3 years, three identical experiments with group-housed rats were performed. At the beginning of each experiment, wbSARs ranged from 32.5 to 130 mW/kg; wbSARs at 11 months ranged from 15 to 60 mW/kg; on average, wbSARs ranged from 17.5 to 70 mW/kg. Rats were killed when mammary-gland tumours reached 1–2 cm in diameter, and tumours were evaluated histopathologically. The incidence of benign or malignant mammary-gland tumours did not differ between sham-exposed and exposed groups. A statistically significant delay in the appearance of mammary-gland adenocarcinoma was seen in RF-exposed rats in the first experiment; this effect was not confirmed in the second or third experiment (Bartsch *et al.*, 2002). [The Working Group noted the lack of reproducibility in tumour response between the three experiments.]

Two experiments were performed with the same GSM signal at 900 MHz as mentioned above, but with different intensities. In both experiments, groups of 16 female Sprague-Dawley rats were

sham-exposed or exposed to GSM RF radiation for 9 weeks, starting 10 days after administration by gastric intubation of 10 mg of DMBA at the age of 55 days, and were observed for an additional 3 weeks. In the first experiment, groups were exposed at wbSAR 0 (sham), 1.4, 2.2, or 3.5 mW/g and the authors reported that mammary-gland tumours developed more rapidly in rats exposed to signals at wbSAR 1.4 and 2.2 mW/g compared with controls. In the second experiment, groups were exposed at wbSAR 0 (sham), 0.1, 0.7, or 1.4 mW/g, and a decreased incidence of malignant mammary-gland tumours was seen in the group exposed to the signal at a wbSAR of 1.4 mW/g. Overall, no differences in the latency, multiplicity, or volume of mammary-gland tumours were observed (Anane *et al.*, 2003). [The Working Group noted that the value of this study was reduced by the lack of reproducibility between exposure to RF radiation and mammary-gland tumour responses.]

Groups of 99–100 female Sprague-Dawley rats (age, 48 days) were given DMBA as a single oral dose of 35 mg/kg bw, followed by sham-exposure or exposure to RF radiation as a GSM signal at 900 MHz, for 4 hours per day, 5 days per week, for 26 weeks, in a Ferris wheel/tube-restrained system. Values for wbSAR were 0 (sham), 0.44, 1.33, and 4.0 mW/g. A cage-control group was also included. No differences in body weight, or in the incidence, latency to onset, multiplicity, or size of mammary-gland tumours were seen in this study (Yu *et al.*, 2006).

In an experiment with a design very similar to that of Yu *et al.* (2006), groups of 100 female Sprague-Dawley rats (age, 46–48 days) were given DMBA as a single oral dose of 17 mg/kg bw, followed 1–2 days later by sham-exposure or exposure to RF radiation as a GSM signal at 900 MHz (pulse, 217 Hz), for 4 hours per day, 5 days per week, for 6 months, in a Ferris wheel/tube-restrained system. Values for wbSAR were 0 (sham), 0.4, 1.3, and 4.0 mW/g. A cage-control group was also included. Exposure to RF radiation had no effect on survival or body weight. When compared with the sham-exposed control group, the group at 4.0 mW/g demonstrated a statistically significant increase in the number of rats with malignant mammary-gland tumours (mainly adenocarcinomas) and a significant decrease in the number of rats with benign mammary-gland tumours (Hruby *et al.*, 2008). [The Working Group noted that incidences of mammary-gland cancer were similar in the group at 4.0 mW/g and in the cage-control group.]

3.2.4 Brain-tumour model

Groups of pregnant F344 rats received *N*-ethyl-*N*-nitrosourea (ENU) as a single intravenous dose at 4 mg/kg bw on day 18 of gestation. From day 19 of gestation to postnatal day 21, the pregnant dams and offspring were exposed to far-field RF radiation as an NDAC (North American Digital Cellular)-modulated signal at 836.55 MHz for 2 hours per day, 7 days per week. On postnatal day 33/35, the offspring were sham-exposed or exposed to intermittent near-field RF radiation, 2 hours (8 × 7.5 minutes field on/off) per day, 4 days per week. The total duration of the near-field plus far-field exposure was 24 months. The head region of each rat was exposed to near-field RF radiation in a Ferris wheel/tube-restrained system. Calculated SAR values in the brain ranged from 1.1–1.6 mW/g. The study included four groups: group 1 was sham-exposed (30 males, 30 females); group 2 was exposed to RF radiation (30 males, 30 females); group 3 was ENU/sham-exposed (30 males, 30 females); and group 4 was ENU/RF-exposed (30 males, 26 females). No statistically significant differences in the incidence of tumours of the brain or spinal cord were observed in the sham-exposed and RF-exposed groups (Adey *et al.*, 1999).

The same laboratory performed a second study with a similar design in pregnant F344 rats exposed to ENU, the offspring of which then became treatment cohorts in six groups. Group

1 was sham-exposed (45 males and 45 females per group); group 2 was RF-exposed (45 males and 45 females per group); group 3 was ENU/sham-exposed (45 males and 45 females per group); group 4 was ENU/RF-exposed (38 males, 52 females); group 5 was exposed to ENU and served as cage control (45 males and 45 females per group); and group 6 served as cage control (45 males and 45 females per group). Treatment with ENU on day 18 of gestation and exposure to far-field RF radiation (2.6 ± 0.50 W/cm^2) from day 19 of gestation to postnatal day 21 was identical to that described in Adey *et al.* (1999). Sham exposure or exposure to near-field RF radiation (836.55 MHz, "balanced speech" modulation; brain SAR, 1.1–1.6 mW/g) for 2 hours per day, 4 days per week, began on postnatal day 31. The total duration of the near-field plus far-field exposure was 24 months. No statistically significant differences were identified in the incidence or histological type of tumours of the brain and spinal cord in the RF-exposed and sham-exposed groups (Adey *et al.*, 2000).

Pregnant F344 rats received ENU as a single intravenous dose at 4 mg/kg bw on day 18 of gestation. Offspring were randomized into groups of 50 males and 50 females as follows: group 1 was a cage-control group; group 2 was exposed to ENU only; group 3 was exposed to ENU and sham-exposed to RF radiation; group 4 was exposed to ENU and exposed to RF radiation at a low level (brain averaged SAR, 0.67 mW/g); and group 5 was exposed to ENU and exposed to RF radiation at a high level (brain averaged SAR, 2.0 mW/g). Offspring received "head-only" exposure to near-field RF radiation (1439 MHz, TDMA signal), 90 minutes per day, 5 days per week, until age 104 weeks. Exposure to TDMA-modulated RF radiation had no effect on the survival or body weight of rats treated with ENU. Comparisons of the incidences of tumours of the brain and spinal cord in rats treated with ENU did not reveal any statistically significant effects of exposure to TDMA RF radiation (Shirai *et al.*, 2005).

A second study was performed by the same laboratory, with a design that was essentially identical to that described in Shirai *et al.* (2005). Pregnant F344 rats received ENU as a single intravenous dose at 4 mg/kg bw on day 18 of gestation. Offspring were randomized into groups of 50 males and 50 females as follows: group 1 was a cage-control group; group 2 was exposed to ENU only; group 3 was exposed to ENU and sham-exposed; group 4 was exposed to ENU and exposed to RF radiation at a low level (brain averaged SAR, 0.67 mW/g); and group 5 was exposed to ENU and exposed to RF radiation at a high level (brain averaged SAR, 2.0 mW/g). Offspring received "head-only" exposure to near-field RF radiation as a WCDMA (wide-band code-division multiple access) signal at 1.95 GHz from cell phones for IMT-2000 (International Mobile Telecommunication) cellular systems, for 90 minutes per day, 5 days per week, until age 104 weeks. Exposure to RF radiation had no effect on the survival or body weight of rats treated with ENU. Comparisons of the incidences of tumours of the brain and spinal cord in rats treated with ENU did not reveal any statistically significant effects of exposure to WCDMA RF radiation (Shirai *et al.*, 2007).

Pregnant Sprague-Dawley rats received ENU by intravenous injection at a dose of 0, 2.5 or 10 mg/kg bw on day 15 of gestation. Beginning on postnatal day 57, groups of offspring were sham-exposed or exposed to RF radiation in a Ferris wheel/tube-restrained system for 6 hours per day, 4 days per week for 22 months. RF metrics tested included a pulsed-wave signal (PW) at 860 MHz and a continuous-wave signal (CW) at 860 MHz. Average brain SAR was 1.0 mW/g for both. Including cage controls, the entire experiment consisted of 15 groups of 30 males and 30 females. Key groups included ENU plus sham-exposure; ENU plus PW exposure; and ENU plus CW exposure. Detailed data regarding

treatment and tumour incidences are tabulated in Table 3.2. The results of this study provided no statistically significant evidence that exposure to PW or to CW increased the incidence of tumours in any of the tissues studied, or that it promoted the induction of cranial or spinal-cord tumours initiated by ENU (Zook & Simmens, 2001).

In a follow-up study by the same authors, pregnant female Sprague-Dawley rats received ENU as a single intravenous dose at 6.25 or 10.0 mg/kg bw on day 15 of gestation. Offspring were randomized by ENU-dose into groups of 90 males and 90 females and then, as in the previous study, exposed to RF radiation from postnatal day 52 ± 3 as a PW signal at 860 MHz, in a Ferris wheel/tube-restrained system, 6 hours per day, 5 days per week, at an average brain SAR of 1.0 mW/g. The study was terminated when the offspring were aged 24 months. Each group included three cohorts and the study was conducted in three phases, each containing six groups. Groups 1, 2, and 3 received ENU at 6.25 mg/kg bw plus: (i) sham exposure to RF radiation (group 1); or (ii) exposure to RF radiation (group 2); or (iii) no treatment (cage control; group 3); while groups 4, 5 and 6 received ENU at 10.0 mg/kg bw plus: (i) sham exposure to RF radiation (group 4); or (ii) exposure to RF radiation (group 5); or (iii) no treatment (cage control; group 6). Necropsies were performed monthly on selected rats from each group, beginning at age 171 days. Exposure to RF radiation had no statistically significant effects on the survival or body weight of rats treated with ENU. Histopathological evaluation of tissues from the nervous system provided no evidence that exposure to the RF signal affected the incidence, multiplicity or latency of any type of neurogenic tumour (Zook & Simmens, 2006).

3.3 Co-carcinogenesis

See Table 3.3

To evaluate the possible effects of RF-radiation exposure on colon carcinogenesis, three groups of 26–32 male and 26–32 female BALB/c mice (age, 4–5 weeks) were given dimethylhydrazine (DMH) as a subcutaneous injection at a dose of 15 mg/kg bw every week for 14 weeks, and subsequently at a dose of 20 mg/kg bw for 8 weeks. Starting 3 weeks after the first injection of DMH, the mice were either sham-exposed, exposed to RF radiation at 2450 MHz (SAR, 10–12 mW/g) for 3 hours per day, 6 days per week, for 5 months, or given weekly intraperitoneal injections of TPA at 2 μg per mouse for 10 weeks. Mice in the control group were given a subcutaneous injection of saline solution only. The incidences of tumours of the colon were similar in all groups treated with DMH (Wu *et al.*, 1994).

The possible effects of exposure to RF radiation on tumorigenesis were investigated in the offspring of pregnant female $B6C3F_1$ mice treated with ENU. Exposure of pregnant mice to RF radiation as a UMTS signal at 1966 MHz was initiated on day 6 of gestation, and was continued throughout pregnancy and for 2 years post-parturition. Pregnant mice were also intraperitoneally injected with ENU at a dose of 40 mg/kg bw on day 14 of gestation. Groups of 54–60 offspring were exposed to UMTS RF radiation at an intensity of 0, 4.8, or 48 W/m^2 for 20 hours per day, 7 days per week. Group 1 served as a cage control; group 2 was exposed to ENU only; group 3 was sham-exposed only; group 4 was exposed to ENU plus UMTS RF radiation at 4.8 W/m^2; and group 5 was exposed to UMTS RF radiation at 48 W/m^2. Comparable incidences of tumours were seen in the groups that were not exposed to ENU. In groups exposed to ENU, UMTS RF radiation increased the incidence of bronchioloalveolar carcinoma and hepatocellular adenoma (Tillmann *et al.*, 2010). [The Working Group noted that this experimental model had not been used previously in other studies of hazard identification, and its concordance with the human carcinogenic response is unknown.]

Three groups of 45–49 transgenic female K2 mice overexpressing the human ornithine

decarboxylase (*ODC*) gene and their wild-type littermates were exposed to a combination of ultraviolet (UV) radiation and pulsed RF radiation. The UV dose was 240 J/m^2 delivered three times per week for 52 weeks. The mice were sham-exposed or exposed to RF radiation for 1.5 hours per day, 5 days per week, for 52 weeks. One group of mice was exposed to D-AMPS (digital advanced mobile phone system)-modulated RF radiation at 849 MHz; a second group was exposed to GSM RF radiation at 902.4 MHz; and a third group was sham-exposed. Nominal average SAR for both exposed groups was 0.5 mW/g. A cage-control group of 20 mice was included. There were no differences in the cumulative survival or body weight in groups exposed to UV, regardless of exposure to RF radiation. UV exposure induced macroscopic tumours of the skin in 12% of the non-transgenic mice and in 37% of the transgenic mice. Exposure to RF radiation had no effect on the induction of squamous cell carcinoma of the skin in either transgenic or wild-type mice (Heikkinen *et al.*, 2003).

A study evaluated the possible effects of exposure to RF radiation on tumorigenesis induced by the mutagen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(*5H*)-furanone (MX), a by-product of water disinfection. Groups of 72 female Wistar rats (age, 7 weeks) were given drinking-water containing MX at a daily average dose of 0 (cage-control) or 1.7 mg/kg bw for 104 weeks, and were then sham-exposed or exposed to pulsed RF radiation at 900 MHz (wbSARs of 0 [sham control], 0.3 or 0.9 mW/g) in restrainers for 2 hours per day, 5 days per week, for 104 weeks. Exposure to RF radiation had no statistically significant effects on mortality or body weight of rats treated with MX. Compared with the MX-treated sham-exposed control group [but not the cage control group], a statistically significant increase in the incidence of combined vascular tumours (haemangiomas, haemangiosarcomas and lymphangiomas combined) was observed in the mesenteric lymph nodes of the group treated with MX and RF radiation at a high intensity (wbSAR, 0.9 mW/g). Exposure to RF radiation had no significant effect on the incidence of tumours in any other tissue (Heikkinen *et al.*, 2006). [The Working Group noted that this experimental model had not been used previously in other hazard-identification studies, and its concordance with human carcinogenic response is unknown.]

Groups of 40 male BALB/c mice received 10 µL of a 5% solution of benzo[*a*]pyrene by skin painting on alternate days for 5 months, and were exposed to RF radiation as microwaves at 2450 MHz for 2 hours per day, 6 days per week, in an anechoic chamber, according to two different protocols. In the pre-exposure protocol, the mice were exposed to microwave radiation at SARs of 0 mW/g (sham) or 2–3 mW/g for 1 or 3 months before application of benzo[*a*]pyrene. In the simultaneous-exposure protocol, groups of mice were exposed to RF radiation at SARs of 0 mW/g, 2–3 mW/g, or 6–8 mW/g concurrently with administration of benzo[*a*]pyrene. Pre-exposure or simultaneous exposure to microwave radiation at either SAR value accelerated the development of benzo[*a*]pyrene-induced skin cancer. A comparable acceleration of skin tumorigenesis was reported in benzo[*a*]pyrene-treated mice undergoing confinement stress for 1 or 3 months (Szmigielski *et al.*, 1982). [The Working Group noted that the study design and experimental data from this paper were poorly presented and difficult to interpret.]

In a second study performed by the same group, six groups of 100 adult male BALB/c mice were painted with 10 µL of 1% benzo[*a*]pyrene on the interscapular region of the skin on alternate days for 6 months. Two different schedules of exposure to microwave radiation at 2450 MHz were used. In the first experiment, three groups were exposed to microwave radiation (mean wbSAR, 4 mW/g) for 2 hours per day, 6 days per week, for 1, 2 or 3 months before the start of

Table 3.3 Co-carcinogenicity studies in experimental animals exposed to radiofrequency radiation

Species, strain (sex) Carcinogen Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, K2 (*ODC*-transgenic and wild-type) (F) UV radiation: 240 J/m^2, 3 × /wk, 52 wk 52 wk Heikkinen et al. (2003)	DAMPS-type (849 MHz) or GSM-type (902.4 MHz) RF, SAR: 0.5 mW/g 1.5 h/d, 5 d/wk, 52 wk Sham (*ODC*-transgenic + wild-type): 19 + 26; D-AMPS: 20 + 26; GSM: 22 + 27; and cage control: 12 + 8	Squamous-cell carcinoma of the skin: *ODC*-transgenic (sham): 6/19 *ODC*-transgenic (GSM): 5/21 *ODC*-transgenic (DAMPS): 8/20 Wild-type (sham): 2/26 Wild-type (GSM): 4/27 Wild-type (DAMPS): 4/26	NS	Restrained exposure Histopathological evaluation of all skin lesions
Rat, Wistar (F) 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone [MX], 1.7 mg/kg bw, drinking-water, 104 wk 104 wk Heikkinen et al. (2006)	GSM (900 MHz) PW (whole body) with wbSARs of 0.3 mW/g (low RF) or 0.9 mW/g (high RF), sham, cage control 2 h/d, 5 d/wk, 104 wk 72/group	Combined vascular tumours (haemangioma, haemangiosarcoma and lymphangioma) in the mesenteric lymph nodes (cage control, sham, low RF, high RF): 10/72 (14%), 3/72 (4%), 1/72 (1%), 11/72 (15%)	$P < 0.05$ (Fisher test), high RF *vs* sham	Complete histopathology No significant difference between high RF-radiation-exposed group and cage-control group
Mouse, BALB/c (M, F) DMH, 15 mg/kg bw per wk for 14 wk followed by 20 mg/kg bw per wk for 8 wk, i.p. 25 wk Wu et al. (1994)	2 450 MHz MW, 3 h/d, 6 d/wk, 5 mo, 10 mW/cm^2 (SAR, 10–12 mW/g); sham exposure; or TPA promotion (i.p., 2 µg/wk, 10 wk) 3 wk after 1st DMH injection A control group was i.p. injected with saline only 26–32/group	Colon tumours: DMH + sham: 13/28 (46%) DMH + MW: 13/26 (50%) DMH + TPA: 17/32 (53%) Control (saline only): 0/29 Protuberant or invasive colon tumours: DMH + sham: 13.9% DMH + MW: 16.3% DMH + TPA: 44.1%	- NS NS - NS $P < 0.05$	Single housing in small plexiglass cages during MW exposure Tumour bearing mice with total tumour areas > 5 mm^2: 71% in DMH + TPA-treated group ($P < 0.05$) *vs* 31% in DMH- and 31% in DMH + MW-treated groups.
Mouse, B6C3F$_1$ (F) ENU, 40 mg/kg bw i.p., on GD 14 106 wk Tillmann et al. (2010)	1966 MHz, UMTS signal 20 h/d, 7 d/wk, 106 wk (starting on GD 6) 0 (sham), 4.8, 48 W/m^2 SAR: variable Group 1: cage control Group 2: ENU Group 3: sham exposure Group 4: ENU + UMTS (4.8 W/m^2) Group 5: UMTS (48 W/m^2) 54–60/group	Bronchiolo-alveolar adenoma: group 4 (36/58, 62%) *vs* group 2 (27/60, 45%) Bronchiolo-alveolar carcinoma: group 4 (45/58, 78%) *vs* group 2 (33/60, 55%) Hepatocellular adenoma: group 4 (49/58, 85%) *vs* group 2 (30/60, 50%) Hepatocellular carcinoma: group 4 (30/58, 52%) *vs* group 2 (31/60, 52%) Comparable incidences of tumours in group 1, 3 and 5	NS $P < 0.05$ $P < 0.001$ NS	Tissues that were histopathologically evaluated included brain, lungs, liver, spleen, kidneys, mesenteric lymph nodes, and any gross lesions detected.

Table 3.3 (continued)

Species, strain (sex) Carcinogen Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, BALB/c (M) *Exp.1*: 1 or 3 mo irradiation before B[*a*]P skin painting on alternate days for 5 mo *Exp. 2*: 5 mo-irradiation simultaneously with B[*a*]P skin painting on alternate days for 5 mo Up to 12 mo Szmigielski et al. (1982)	2 450 MHz MW (far-field condition in an anechoic chamber) 2 h/d, 6 d/wk Confinement-stress controls were provided: mice were located individually in a chronic stress-syndrome compartment for 1–8 mo. *Exp. 1*: sham, 5 mW/cm^2 (1 mo before B[*a*]P), 5 mW/cm^2 (3 mo before B[*a*]P), confinement stress (1 mo before B[*a*]P), or confinement stress (3 mo before B[*a*]P)	*Exp. 1*: No. of mice with skin cancers: 0, 2, 22*, 3, 16* after 6 mo 4, 18*, 29*, 16*, 25* after 8 mo 19, 27**, 36**, 24, 31** after 10 mo	*$P < 0.01$ **$P < 0.05$	Distance from the antenna (vertical 30 × 30 cm horn antenna) to cages: 220 cm. Four cages (30 × 50 cm area cage) containing 10 mice each. Data are poorly presented and difficult to interpret.
	Exp. 2: sham, 5 mW/cm^2, 15 mW/cm^2 or confinement stress SAR: 2–3 mW/g (5 mW/cm^2) or 6–8 mW/g (15 mW/cm^2) 40/group	*Exp. 2*: Number of mice with skin cancers: 0, 12*, 28*, 13* after 6 mo 5, 23*, 33*, 26* after 8 mo 21, 32*, 38*, 31* after 10 mo	*$P < 0.01$	
Mouse, BALB/c (M) *Exp. 1*: 6 mo irradiation simultaneously with B[*a*]P skin painting *Exp. 2*: 1, 2 or 3 mo irradiation before B[*a*]P skin painting on alternate days for 6 mo Up to 12 mo Szudziński et al. (1982)	2 450-MHz MW (far field) 2 h/d, 6 d/wk	Skin carcinoma		
	Exp. 1: 0, 5 or 15 mW/cm^2, SAR: 0, 2 or 6 mW/g	*Exp. 1*: CDT_{50} of 296, 235, 131 days at 0, 5, 15 mW/cm^2	$P < 0.05$ at 15 mW/cm^2	
	Exp. 2: three groups at 10 mW/cm^2 wbSAR: 4 mW/g 100/group	*Exp. 2*: CDT_{50} of 253, 210, or 171 days after 1, 2 or 3 mo of irradiation [Control CDT_{50}: 296 days, see *Exp. 1*]	No *P*-values reported	No concurrent sham control in *Exp. 2*

B[*a*]P, benzo[*a*]pyrene; CNS, central nervous system; CDMA, code-division multiple access; CDT_{50}, cancer development time 50 (i.e. time in which 50% of the mice developed skin carcinoma); d, day; D-AMPS, digital advanced mobile phone service; DCS, Digital Personal Communication System; DEN, diethylnitrosamine; DMBA, 7,12-dimethylbenz[*a*] anthracene; DMH, dimethylhydrazine; EMF, electromagnetic field; ENU, *N*-ethyl-*N*-nitrosourea; FDMA, frequency-division multiple access; GD, gestational day; GSM, Global System for Mobile communication; i.p., intraperitoneal; i.v., intravenously; MMW, millimetre wavelength; mo, month; MW, microwave; NADC, North American Digital Cellular; NS, not significant; ODC, ornithine decarboxylase; PH, partial hepatectomy; p.o., oral administration; PRF, pulsed radiofrequency field; RF, radiofrequency radiation; SAR (wb, av), (time-averaged whole-body) specific absorption rate; s.c., subcutaneously; TDMA, time-division multiple access; TPA, 12-*O*-tetradecanoylphorbol-13-acetate UMTS, Universal Mobile Telecommunication System; UWB, ultra-wide band; WCDMA, wide-band code-division multiple access; wk, week

benzo[*a*]pyrene application. In the second experiment, three groups were exposed to RF radiation (wbSAR, 0 mW/g [sham-exposed control], 2 mW/g, or 6 mW/g), 2 hours per day, 6 days per week, for 6 months, concurrently with exposure to benzo[*a*]pyrene. Irradiation by either schedule resulted in an acceleration in the development of benzo[*a*]pyrene-induced skin carcinoma and decreased the lifespan of the animals (Szudziński *et al.*, 1982). [The Working Group noted that the study design and experimental data were poorly presented and difficult to interpret. Survival and tumour data from groups receiving pre-exposure to microwave radiation may be invalid due to the lack of concurrent sham-exposed controls.]

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4. OTHER RELEVANT DATA

Data on specific absorption rate (SAR) and distribution of radiofrequency (RF) radiation inside tissues and organs and at the subcellular level are presented elsewhere in this Volume (Section 1.3, Dosimetry).

4.1 Genetic and related effects

4.1.1 Humans

During the past decades, extensive research efforts have focused on determining the extent of DNA damage in eukaryotic and prokaryotic cells exposed to RF radiation. Several published reviews concluded that: (i) the existing data are not sufficiently strong to suggest that RF radiation is directly genotoxic; (ii) exposure to RF radiation probably does not enhance the damage induced by known genotoxic agents; and (iii) some of the reported "adverse effects" may be attributed to hyperthermia induced by RF radiation (Brusick *et al.*, 1998; Verschaeve & Maes, 1998; Moulder *et al.*, 1999, 2005; Heynick *et al.*, 2003; Meltz, 2003; Vijayalaxmi & Obe, 2004; Verschaeve, 2005; Krewski *et al.*, 2007; Lai, 2007; Vijayalaxmi & Prihoda, 2008; Phillips *et al.*, 2009; Rüdiger, 2009a; Verschaeve, 2009; Verschaeve *et al.*, 2010). International organizations and expert scientific advisory groups in several countries, including Canada, France, the Netherlands, Sweden, the United Kingdom and the USA, have reached similar conclusions (ICNIRP, 2009).

This Section of the *Monograph* deals with studies on primary DNA damage in humans exposed occupationally or as mobile-phone users; in these studies DNA damage was measured in peripheral blood lymphocytes and buccal cells by means of the alkaline or neutral single-cell gel electrophoresis assay (comet assay), which reveals alkali-labile lesions and single- and double-strand breaks in DNA, or by use of cytogenetic tests for chromosomal aberrations, micronucleus formation and sister-chromatid exchange (SCE). The studies reviewed below are summarized in Table 4.1 and Table 4.2 (with details of the exposure conditions).

(a) Peripheral blood lymphocytes

(i) Occupational exposure

Garaj-Vrhovac *et al.* (1990a) were the first to report an increased frequency of chromosomal aberrations in the form of chromatid and chromosome breaks, acentric fragments, dicentrics, rings and polycentric chromosomes, as well as micronuclei in 10 individuals employed in a radar service-station facility. The frequency of cells with chromosomal aberrations and micronuclei ranged from 1.6% to 31.5% and from 1.6% to 27.9%, respectively, in exposed subjects, while the corresponding values in controls were 1.8% and 1.5% [no range given].

In a study in Australia, Garson *et al.* (1991) collected lymphocytes from 38 radio linesmen,

Table 4.1 Genetic and related effects of radiofrequency radiation in peripheral blood lymphocytes of occupationally exposed individuals

End-point	No. of subjects	Occupation	Frequency	SAR or power density	Duration	Results	Reference
Aneuploidy	18	Air-traffic controllers; engineers	100 kHz to 300 GHz	-	10–27 yr	+	Othman *et al.* (2001)
CA	10	Radar maintenance workers	0.2 MHz to 26 GHz	0.010–50 mW/cm^2	8–25 yr	+	Garaj-Vrhovac *et al.* (1990a)
CA	38	Radio linesmen	400 kHz to 20 GHz	614 V/m	5 yr	–	Garson *et al.* (1991)
CA	6	Air-traffic radar-repairmen	1250–1350 MHz	0.01–20 mW/cm^2	16 yr	+ [after a 30-wk follow-up, total aberrations had decreased]	Garaj-Vrhovac *et al.* (1993)
CA	6	Transmission-antenna maintenance workers	450–900 MHz	NR	1 yr	–	Maes *et al.* (1995)
CA	20	Workers in telecommunication and radio-relay stations	8 GHz	1 mW/cm^2	6 yr (12 h/d)	+	Lalić *et al.* (2001)
CA	50	Air-traffic controllers, engineers	100 kHz to 300 GHz	NR	8–27 yr	+	Aly *et al.* (2002)
CA	49	Radio engineers	450–900 MHz	NR	2.3 yr (> 1 h/d)	–	Maes *et al.* (2006)
CA	10	Radar maintenance workers	1250–1350 MHz	0.010–20 mW/cm^2	7–29 yr	+	Garaj-Vrhovac & Orescanin (2009)
MN	10	Radar maintenance workers	0.2 MHz to 26 GHz	0.010–50 mW/cm^2	8–25 yr	+	Garaj-Vrhovac *et al.* (1990a)
MN	NR	Multiple occupations	1250–1350 MHz	0.01–20 mW/cm^2	15 yr	+	Fucić *et al.* (1992)
MN	12	Radar maintenance workers	1250–1350 MHz	0.01–20 mW/cm^2	13 yr	+	Garaj-Vrhovac (1999)
SB	40	Flight crew	NR	NR	5–18 yr	–	Cavallo *et al.* (2002)
SB	49	Radio engineers	450–900 MHz	NR	2.3 yr (> 1 h/d)	–	Maes *et al.* (2006)
SB	10	Radar maintenance workers	1250–1350 MHz	0.010–20 mW/cm^2	7–29 yr	+	Garaj-Vrhovac & Orescanin (2009)
SCE	50	Air-traffic controllers	100 kHz to 300 GHz	NR	8–27 yr	–	Aly *et al.* (2002)
SCE	49	Radio engineers	450–900 MHz	NR	2.3 yr (> 1 h/d)	–	Maes *et al.* (2006)

+ increase; –, no effect; CA, chromosomal aberration; d, day; h, hour; MN, micronucleus formation; NR, not reported; SAR, specific absorption rate; SB, DNA single- and double-strand breaks; SCE, sister-chromatid exchange; wk, week; yr, year

Table 4.2 Genetic and related effects of radiofrequency radiation in peripheral blood lymphocytes and buccal cells of mobile-phone users

End-point	No. of subjects	Frequency	SAR	Duration	Results	Reference
Peripheral blood lymphocytes						
CA	24	890–960 MHz	NR	2 yr	+	Gadhia *et al.* (2003)
CA	25	NR	0.1–1.9 W/kg	3–5 yr	+	Gandhi & Singh (2005)
MN	24	800–2000 MHz	0.6–1.6 W/kg	1–5 yr	+	Gandhi & Anita (2005)
SB	24	800–2000 MHz	0.6–1.6 W/kg	1–5 yr	+	Gandhi & Anita (2005)
SCE	24	890–960 MHz	NR	2 yr	+	Gadhia *et al.* (2003)
Buccal cells						
MN	25	NR	0.1–1.9 W/kg	3–5 yr	+	Gandhi & Singh (2005)
MN	85	NR	0.3–1.0 W/kg	2.3 yr (1 h/d)	+	Yadav & Sharma (2008)
MN	112	NR	NR	5–10 yr (3 h/wk)	–	Hintzsche & Stopper (2010)

+, increase; –, no effect; CA, chromosomal aberration; d, day; h, hour; MN, micronucleus formation; NR, not reported; SAR, specific absorption rate; SB, DNA single- and double-strand breaks; SCE, sister-chromatid exchange; wk, week; yr, year

who erected and maintained broadcasting, telecommunication and satellite RF-transmission towers, and found no increase in the frequency of chromosomal aberrations compared with the frequency in 38 controls working as clerical staff. In this study, exposure to RF radiation was at or below occupational limits for Australia.

Fucić *et al.* (1992) measured the surface area of micronuclei in lymphocytes of workers in multiple occupations exposed to pulsed microwaves, X-rays (< 25 mSv during the previous 2 years) and vinyl-chloride monomer (VCM; average concentration, 50 ppm). The sample size in each category was not mentioned in the paper. There were increased numbers of smaller micronuclei in individuals exposed to X-rays and VCM, indicating a clastogenic effect. Increased numbers of smaller as well as larger micronuclei were found in individuals exposed to microwaves, suggesting a dual role of this type of radiation, as clastogen and aneugen.

In a regular 30-week follow-up investigation of six individuals who were acutely exposed to pulsed-wave RF radiation of high power density at an air-traffic radar-repair station, Garaj-Vrhovac *et al.* (1993) observed a decline in the total number of chromosomal aberrations.

A preliminary study conducted by Maes *et al.* (1995) involved six workers in charge of maintaining transmission antennae linked to a mobile-phone network, and six matched controls. No increase in the frequency of chromosomal aberrations was observed in the maintenance workers. The authors mentioned the limited size of the study and the fact that exposure to RF radiation was intermittent. They then extended the study to 49 professionally employed radio engineers working in the field, and 11 administrative staff. Some of these had participated in the earlier study. No differences between exposed and controls were observed with the alkaline comet assay, the assay for chromosomal aberration, or the test for SCE (Maes *et al.*, 2006).

Garaj-Vrhovac (1999) examined 12 subjects employed in repair services for radar equipment and antennae, and reported frequencies of 8–23 micronuclei per 500 cells in exposed workers compared with 2–7 per 500 cells in control subjects; this difference was statistically significant.

Lalić *et al.* (2001) investigated 20 workers in telecommunication and radio-relay stations who were exposed to non-ionizing electromagnetic fields, and 25 subjects employed as X-ray technicians, nurses and engineers in radiology, exposed to ionizing radiation. The analysis indicated an increased frequency of chromosomal aberration in both groups. The incidence of dicentric chromosomes was higher in the group exposed to non-ionizing radiation than in the group exposed to ionizing radiation.

Othman *et al.* (2001) studied professional air-traffic controllers and engineers exposed to RF radiation emitted by different pieces of equipment at the workplace. In a first study, blood lymphocytes were collected from 18 workers and 5 unexposed controls (all males), and cultured for 72 hours. Fluorescence *in situ* hybridization (FISH) with repetitive α-satellite probes for chromosomes 7, 12, 17, and the heterochromatic region of the Y-chromosome, was used to determine the number of aneuploid cells. The results showed increased frequencies of monosomic cells containing a single copy of chromosome 7 (6.6%) or 17 (6.1%), and of cells lacking the Y-chromosome (8.4%): the corresponding values for the controls were 3.2%, 3.7% and 4.5%, respectively.

In a further study by the same group, Aly *et al.* (2002) examined lymphocytes from 26 air-traffic controllers, 24 engineers and 10 controls. Conventional cytogenetic techniques revealed an increase in the frequency of structural aberrations (2.7–5.3%) and numerical aberrations (8.9–9.3%) in exposed individuals relative to controls (0.8% and 3.2%, respectively). In subjects exposed to RF radiation, 90% of the cells were hypodiploid, i.e. showed loss of chromosomes. The frequency of SCE was also increased, but this increase did not reach statistical significance. [The Working Group noted that conventional cytogenetic techniques may be less reliable than the FISH technique for counting numerical aberrations.]

Cavallo *et al.* (2002) studied 40 airline pilots and flight technicians exposed to cosmic rays, electromagnetic fields from radar equipment, pollutants from jet-propulsion fluid etc. and 40 non-exposed individuals working on the ground. In the comet assay, visual examination of the results revealed a small increase in the frequency of DNA strand breaks in exposed individuals compared with ground staff, but this increase was not statistically significant.

Garaj-Vrhovac & Orescanin (2009) used the comet assay to measure DNA strand breaks and the test for sensitivity to bleomycin described by Michalska *et al.* (1998) to investigate genomic instability in 10 individuals working in radar-equipment and antenna-system services, and in 10 control subjects. In the latter method, the cells were treated with bleomycin (a drug used in clinical treatment of cancer) during the last 5 hours before harvesting after a culture period of 72 hours, to assess the incidence of chromosomal aberrations in the form of chromatid breaks. The results of the comet assay revealed increased DNA damage (tail length, 17.1 μm, and tail moment, 14.4, in the exposed individuals compared with 14.2 μm and 11.7, respectively, in the controls). The test for sensitivity to bleomycin showed a higher number of chromatid breaks (1.7 per cell in the exposed, compared with 0.5 per cell in the controls). All these differences were statistically significant.

[The Working Group noted the following limitations in the above-mentioned studies. Exposure assessment was poor or was not mentioned in many reports. The sample size in terms of number of individuals or number of cells analysed was not sufficient to allow robust statistical analysis. Except in one study, "blind" evaluation of microscope slides, and inclusion of positive controls (subjects or cells) while culturing the lymphocytes *in vitro*, was either not performed or not reported. Several investigations were conducted with blood samples collected from workers in one radar-service

facility in Croatia; it was unclear whether the same individuals had been included in more than one of these studies.]

[Although the reports from Australia (Garson *et al.*, 1991) and Belgium (Maes *et al.*, 1995) indicated no effect on the frequency of chromosomal aberrations from exposure to RF radiation, the Working Group noted that situations and exposure conditions in those countries may not have been comparable to those in other countries. Chromosomal changes are highly variable during carcinogenesis and are generally grouped into two categories: (i) reciprocal and balanced structural rearrangements resulting in translocations; and (ii) unbalanced and nonreciprocal structural or numerical changes in which genetic material may be lost or added: the latter can range from a single base pair to the entire chromosome. In the studies reviewed above, reciprocal and balanced structural rearrangements were either not observed or not reported in individuals exposed to RF radiation.]

(ii) Personal exposure from mobile phones

Gadhia *et al.* (2003) collected samples of peripheral blood from 24 users of digital mobile phones and 24 matched controls. Both groups comprised 12 nonsmokers/nondrinkers and 12 smokers/alcoholics [smokers consumed 10–15 cigarettes per day; data on alcohol consumption were not given]. Cytogenetic analysis of lymphocytes cultured for 72 hours indicated a significantly increased incidence ($P < 0.05$) of chromatid gaps and dicentric chromosomes among mobile-phone users who smoked and drank alcohol, but not in nonsmokers/nondrinkers. A significantly increased frequency ($P < 0.05$) of SCE was seen in mobile-phone users of both categories.

Gandhi & Singh (2005) studied G-banded chromosomes in lymphocytes (cultured for 72 hours) from 25 users of mobile phones and 25 non-users. There was a statistically significant increase in the frequency of aberrant metaphases, including triploid chromosomes, acrocentric associations and centromere separation in lymphocytes of mobile-phone users (31.3%) compared with non-users (10.7%). In a subsequent study, Gandhi & Anita (2005) investigated DNA strand breaks by use of the comet assay in lymphocytes from 24 mobile-phone users and 10 controls. Unstimulated lymphocytes were also examined to record the frequency of micronuclei in 20 of those users and 8 non-users. In mobile-phone users, the frequency of damaged cells was 40%, with an average comet-tail length of 27 μm (determined by visual examination with a micrometer), while these values were lower in non-users, at 10% and 8 μm, respectively; both differences were highly significant. The total number of micronuclei was 100 in 40 000 cells in users, and 8 in 16 000 cells in non-users, *i.e.* 2.5% in the former and 0.5% in the latter ($P < 0.05$). [The Working Group noted that the observations reported by Gandhi & Singh (2005) and Gandhi & Anita (2005) were questioned by others (Vijayalaxmi *et al.*, 2007), pointing out several inconsistencies and weaknesses in laboratory methods, data collection, exposure assessment, etc. in both publications.]

(b) Buccal cells: personal exposure from mobile phones

The oral cavity is within the range of RF emissions from mobile phones used at the ear. Hence, examination of the cells in this region is relevant to evaluation of genotoxicity. The oral mucosa has a rich blood supply and is relatively permeable. It has an outer layer of stratified squamous epithelium that is approximately 40–50 cell-layers thick. These exfoliating cells can easily be obtained by non-invasive procedures (oral swabs) from adults, adolescents and children. The turnover of these cells is estimated at 1–3 weeks (Harris & Robinson, 1992).

The frequency of micronuclei in exfoliated buccal cells has been investigated in mobile-phone users. Gandhi & Singh (2005) collected

buccal cells from 25 mobile-phone users and 25 non-users. The average frequencies of micronuclei (in %) were 0.82 ± 0.09 in users and 0.06 ± 0.003 in non-users ($P < 0.05$). [The Working Group noted the same limitations for this study as those mentioned above.]

Yadav & Sharma (2008) collected buccal cells from 85 mobile-phone users and 24 controls. In a total of 1000 cells from each donor, the frequency of micronuclei was determined, along with other indications of degeneration, i.e. karyolysis, karyorrhexis, "broken egg" effect, and binucleate cells. The mean frequency in users (10.7 per 1000 cells) was significantly higher than that in non-users (4.0 per 1000 cells). The changes in incidence of other end-points were not statistically significant. There was also a positive, albeit non-significant, correlation of the total number of micronuclei with increased duration of mobile-phone use.

Hintzsche & Stopper (2010) determined the frequency of micronuclei in buccal cells from 112 mobile-phone users and 13 non-users. Four patients receiving radiotherapy were included as positive controls, along with four healthy controls. The average frequency of micronucleus formation in users was not different from that in non-users. Also, there was no difference when the users were subdivided according to the number of hours of use per week and duration of use of up to 10 years. In contrast, the frequency of micronucleated cells in patients receiving radiotherapy was 131 ± 29.1 per 1000 cells. The authors mentioned that the larger number of individuals studied, the use of DNA-specific staining, and the genotypic variation in the study populations may have contributed to the discrepancy between their results and those of Yadav & Sharma (2008).

[The Working Group noted that counting of 2000 differentiated cells and 200 basal cells is recommended for studies using buccal cells, (Thomas & Fenech, 2011); this was not accomplished in the studies discussed above. Known confounding factors such as tobacco smoking and alcohol consumption were mentioned in some of the studies, but in view of the limited sample size the influence of such factors on the observed abnormalities is difficult to determine.]

[The Working Group further noted that studies of genotoxicity in humans exposed to RF radiation have been carried out by a limited number of research groups; that methodological weaknesses were found in many studies; and that confounding factors were generally not addressed. Overall, although there were studies with positive results for genotoxicity associated with occupational exposure to RF radiation or with the use of mobile phones, the Working Group concluded that the available evidence was not strong enough to draw firm conclusions.]

4.1.2 *Experimental systems:* in vivo

The studies on experimental animals exposed to RF radiation were not uniformly clear in describing the rationale for choosing a specific dose.

(a) Drosophila melanogaster

Adult male fruit flies (*Drosophila melanogaster*) were exposed to RF radiation at either 146.34 MHz produced by a transmitter of 20 W, or 29.00 MHz produced by a transmitter of 300 W, for 12 hours (Mittler, 1976). Loss of the X or Y chromosomes, nondisjunction, and the induction of sex-linked recessive lethal mutations were investigated. There was no significant difference between exposed and non-exposed flies for any of these end-points.

In a subsequent study (Mittler, 1977), *D. melanogaster* were exposed to RF radiation at 98.5 MHz (field strength, 0.3 V/m) for 32 weeks. No significant difference in the incidence of sex-linked recessive lethal mutations was observed in the exposed group compared with the controls.

Hamnerius *et al.* (1979) examined the effect of exposure to RF radiation on somatic mutation of genes involved in eye pigmentation in

D. melanogaster. When embryos were exposed to continuous-wave RF radiation at 2450 MHz (average SAR, 100 W/kg) for 6 hours, no evidence of mutagenicity was found. The same investigators used the same test system to examine mutation frequency in *D. melanogaster* under different conditions of exposure for 6 hours: continuous-wave radiation at 2.45 GHz, pulsed-wave radiation at 3.1 GHz, and continuous-wave magnetic or electric fields at 27.12 MHz. Under none of these conditions was a change in mutation frequency observed (Hamnerius *et al.*, 1985).

Marec *et al.* (1985) investigated the effect of repeated exposures to RF radiation on sex-linked recessive lethal mutations in *D. melanogaster* exposed to continuous-wave RF radiation at 2375 MHz (SAR values: 15 W/cm^2 for 60 minutes per day; or 20 W/cm^2 for 10 minutes per day; or 25 W/cm^2 for 5 minutes per day) for five consecutive days. The mutation frequency in the groups exposed to RF radiation was not significantly different from that in the control group.

In a series of studies from Greece, adverse effects were reported on the reproduction of *D. melanogaster* after exposure to RF radiation at non-thermal mobile-phone frequencies (900 or 1800 MHz). In these experiments commercially available mobile phones were used as exposure devices. The exposures were conducted with the mobile-phone antenna outside the glass vials containing the flies, either in contact with or at a certain distance from the glass wall. The daily duration of exposure varied from 1 to 20 minutes, depending on the experiment. Exposure always started on the day of eclosion and lasted for a total of 5 or 6 days. The temperature within the vials during exposure was monitored with a mercury thermometer with an accuracy of 0.05 °C. The authors explained the decreased reproductive ability as the result of RF radiation-induced DNA fragmentation in the gonads (Panagopoulos, 2011; Panagopoulos & Margaritis, 2008, 2010a, b; Panagopoulos *et al.*, 2004, 2007, 2010).

[In reviewing these studies with *Drosophila*, the Working Group noted several shortcomings related to the methods of exposure assessment and temperature control, which could have influenced the results.]

(b) Mouse

See Table 4.3

(i) 900 MHz

Sykes *et al.* (2001) studied somatic intrachromosomal recombination in the spleen of transgenic pKZ1 mice exposed to pulsed-wave RF radiation at 900 MHz (SAR, 4 W/kg) for 30 minutes per day, for 1, 5, or 25 days. There was a significant reduction in inversions below the spontaneous frequency in the group exposed for 25 days, whereas no effect was found in mice exposed for 1 or 5 days. The authors indicated that the number of mice in each treatment group in this study was small, and that repetition of this study with a larger number of mice was therefore required to confirm these observations.

Aitken *et al.* (2005) found a significant genotoxic effect on the epididymal spermatozoa of CD1 Swiss mice exposed to low-level RF radiation at 900 MHz (SAR, 0.09 W/kg) for 12 hours per day, for 7 days. No impact on male germ-cell development was observed. [The Working Group noted that insufficient information on dosimetry was provided in this study, which prevented a complete evaluation.]

Two cytogenetic studies were conducted with mice exposed to RF radiation from a mobile phone, with or without coexposure to X-rays or ultraviolet (UV) light. In the first study, female CBA/S mice were exposed for 78 weeks (1.5 hours per day, 5 days per week) either to continuous-wave RF radiation at 902.5 MHz (whole-body SAR, 1.5 W/kg) similar to that emitted by analogue NMT (Nordic Mobile Telephony) phones, or to a pulsed-wave signal at 902.4 MHz (SAR, 0.35 W/kg) similar to that emitted by digital GSM phones. All mice, except

the cage controls, were also exposed to X-rays (3 × 1.33 Gy; interval, 1 week) for the first 3 weeks of this experiment. In the second study, female transgenic mice (line K2) and their non-transgenic littermates were exposed to one of two digital mobile-phone signals at a frequency of 849 MHz GSM or 902 MHz DAMPS (Digital Advanced Mobile Phone System), with a SAR of 0.5 W/kg, for 1.5 hours per day, 5 days per week, for 52 weeks. All mice in the second study, except the cage controls, were also exposed to UV radiation mimicking the solar spectrum at 1.2 times the human minimal erythema dose (MED, 200 J/m^2), three times per week. The results did not show any effects of RF fields on frequency of micronuclei in polychromatic erythrocytes or normochromatic erythrocytes, either alone or in combination with X-rays or UV radiation. The results were consistent in the two mouse strains (and in a transgenic variant of the second strain), after 52 or 78 weeks of exposure, at three SAR levels relevant to human exposure from mobile phones, and for three different mobile signals (Juutilainen *et al.*, 2007).

(ii) 900 and 1800 MHz

In a study in B6C3F$_1$ mice exposed to RF radiation at 900 MHz or 1800 MHz (2 hours per day, for 1 week or 6 weeks) at different intensities (with SARs up to 33.2 W/kg in the 1-week experiment, and 24.9 W/kg in the 6-week experiment), the frequency of micronuclei was not increased in erythrocytes of peripheral blood or bone marrow, in keratinocytes or in spleen lymphocytes of the exposed animals compared with controls (Görlitz *et al.*, 2005).

In a long-term study, micronucleus formation was measured in erythrocytes of B6C3F$_1$/CrlBR mice exposed to RF radiation at 902 MHz GSM or 1747 MHz (DCS, Digital Cellular System), at SARs of 0.4, 1.3 or 4.0 W/kg, for 2 hours per day, 5 days per week, for 2 years. No differences were found in the frequencies of micronuclei in exposed, sham-exposed or cage-control mice (Ziemann *et al.*, 2009).

(iii) 1500 MHz

Male Big Blue mice, which are transgenic for the *lacI* marker gene, were locally exposed (in the head region) to near-field RF radiation at 1500 MHz with SARs of 0.67 or 2.0 W/kg, for 90 minutes per day, 5 days per week, for 4 weeks. There was no significant difference between exposed and control mice in the frequency of mutation in the *lacI* transgene in the brain (Takahashi *et al.*, 2002).

(iv) 450 MHz

Sarkar *et al.* (1994) found significant alterations in the length of a DNA microsatellite sequence in the brain and testes of Swiss albino mice exposed to RF radiation at 2450 MHz (power level, 1 mW/cm^2; SAR, 1.18 W/kg) for 2 hours per day, for 120, 150 or 200 days. The authors hypothesized that a DNA fragment (7.7 kb) – generated by the restriction enzyme Hinf1 – that was found after exposure could represent a hypermutable locus and that exposure to these microwaves may have led to amplification of tandem sequences, generating more copies of 5′-GACA-3′ sequences in this particular region. The authors also indicated that the radiation dose applied in the study was close to the prescribed safe limit for population exposure, according to Guidelines of the International Radiation Protection Association at the time (IRPA, 1988).

C3H/HeJ mice were exposed continuous-wave RF radiation at 2450 MHz in circularly polarized wave-guides (average whole-body SAR, 1.0 W/kg) for 20 hours per day, 7 days per week, for 18 months. Peripheral-blood and bone-marrow smears were examined for the presence of micronuclei in polychromatic erythrocytes. The initial publication reported no difference in micronucleus formation between exposed and sham-exposed mice, but a subsequent correction indicated that there was a slight but significant increase in the incidence of micronucleated cells in peripheral-blood and bone-marrow smears

of mice receiving long-term exposure to this RF radiation (Vijayalaxmi *et al.*, 1997a, 1998).

Pregnant *lacZ*-transgenic mice (Muta™Mouse) were exposed (16 hours per day) to intermittent (10 seconds on, 50 seconds off) RF radiation at 2450 MHz with an average whole-body SAR of 0.71 W/kg (4.3 W/kg during the exposure periods of 10 seconds), daily between day 0 and day 15 of gestation. Offspring were examined at age 10 weeks. Mutation frequencies at the *LacZ* gene in the spleen, liver, brain, and testis were similar to those observed in offspring of sham-exposed mice (Ono *et al.*, 2004).

(v) 42 GHz (millimetre waves)

Adult male BALB/c mice were exposed (30 minutes per day) in the nasal region to RF radiation at 42 GHz (incident power density, 31.5 mW/cm^2; peak SAR, 622 W/kg), on three consecutive days. The frequency of micronuclei in peripheral blood and in bone marrow was not increased in exposed mice compared with sham-exposed controls. One group of mice received a single injection of cyclophosphamide (15 mg/kg bw) immediately after the exposure to RF radiation on day 2. The micronucleus frequency in this group was not different from that in mice treated with cyclophosphamide only (Vijayalaxmi *et al.*, 2004).

(vi) Ultra-wide band EMF

Male CF1 mice were exposed for 15 minutes to ultra-wide band (UWB) electromagnetic fields (600 pulses per second) at an estimated whole-body average SAR of 37 mW/kg. The mice were killed at 18 hours or 24 hours after exposure, and peripheral blood and bone marrow were collected and examined for the presence of micronuclei in polychromatic erythrocytes. Under the experimental conditions of this study, there was no evidence of cytogenetic effects in blood or bone marrow of the exposed mice (Vijayalaxmi *et al.*, 1999).

(c) Rat

See Table 4.3

(i) 834 MHz

Micronucleus formation was investigated in the offspring of rats exposed to RF radiation. Wistar rats were placed in experimental cages on the first day of pregnancy and exposed (8.5 hours per day) to RF radiation at 834 MHz (26.8–40 V/m; vertical polarization; peak power, 600 mW; calculated SAR, 0.55–1.23 W/kg) from an analogue mobile telephone that was placed close to the plexiglass cage. Exposure was continued throughout gestation. Newborn pups (age, 2 days) showed a statistically significant increase ($P < 0.003$) in micronucleus frequency in erythrocytes (1.23 ± 0.17 per 1000 cells) compared with controls (0.5 ± 0.1 per 1000 cells). Oxidative parameters measured in blood plasma or liver were not different between exposed and control rats (Ferreira *et al.*, 2006).

(ii) 900–915 MHz

Wistar rats were exposed to RF radiation at 910 MHz (maximum SAR, 0.42 W/kg) for 2 hours per day on 30 consecutive days. Compared with non-exposed control rats, an almost threefold increase in the frequency of micronuclei was found in polychromatic erythrocytes of males and females ($P < 0.001$ and $P < 0.01$, respectively); the induction was significantly lower in females than in males ($P < 0.001$). An increase in micronucleus frequency was also observed in polymorphonuclear cells (Demsia *et al.*, 2004).

Genotoxic effects of coexposure to RF radiation at 900 MHz with 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX, a by-product of water chlorination; 19 µg/ml in drinking-water) were investigated in female Wistar rats (Verschaeve *et al.*, 2006). The rats were exposed to RF radiation for 2 hours per day, 5 days per week, for 2 years, at an average SAR of 0.3 or 0.9 W/kg; exposure to MX was continuous. Blood samples were collected at 3, 6 and 24

Table 4.3 Genetic and related effects of radiofrequency radiation, alone or in combination with chemical/physical mutagens: studies in experimental animals *in vivo*

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
Mouse							
MN formation in peripheral blood and bone-marrow cells in tumour-prone C3H/HeJ mice	2450 MHz, CW	1.0 W/kg	20 h/d, 7 d/wk, for 1.5 yr	None	+	Corrected statistical analysis in 1998 paper	Vijayalaxmi *et al.* (1997a, 1998)
MN formation in PCEs from peripheral blood and bone marrow of CF1 mice	Ultra-wide band radiation	0.037 W/kg	15 min	None	–		Vijayalaxmi *et al.* (1999)
MN formation in peripheral-blood and bone-marrow cells of male BALB/c mice	42 200 MHz	622 ± 100 W/kg	30 min/d for 3 consecutive days	Coexposure with cyclophosphamide	–	No effect of RF radiation alone; no effect on MN induced by cyclophosphamide	Vijayalaxmi *et al.* (2004)
MN formation in erythrocytes of blood or bone marrow, in keratinocytes and in spleen lymphocytes of B6C3F$_1$ mice	900 MHz (GSM) and 1800 MHz (DCS); AM	3.7, 11 and 33.2 W/kg (1-wk study); and 2.8, 8.3 and 24.9 W/kg (6-wk study)	2 h/d during 1 or 6 wk	None	–		Görlitz *et al.* (2005)
MN formation in erythrocytes of female inbred CBA/S mice (taken from study by Heikkinen *et al.*, 2001)	902.5 MHz (NMT), CW or 902.5 MHz (GSM), PW	1.5 W/kg or 0.35 W/kg	1.5 h/d, 5 d/wk, for 78 wk	Also exposed to X-rays (3 × 1.33 Gy, during first 3 wk)	–	No effect of RF radiation alone; no effect on MN induced by X-rays	Juutilainen *et al.* (2007)
MN formation in erythrocytes of female K2 transgenic and non-transgenic mice (taken from Heikkinen *et al.*, 2003)	Digital mobile-phone signals, GSM at 849 MHz and DAMPS at 902 MHz	0.5 W/kg	1.5 h/d, 5 d/wk, for 52 wk	Also exposed to UV radiation (1.2 MED), 3×/wk	–	No effect of RF radiation alone; no effect on MN induced by UV	Juutilainen *et al.* (2007)
MN formation in erythrocytes of B6C3F$_1$/CrlBR male and female mice	GSM (902 MHz) or DCS (1747 MHz)	0.4, 1.3 or 4.0 W/kg	2 h/d, 5 d/wk, for 2 yr	None	–	No difference in MN frequency in exposed, sham-exposed or cage-control mice	Ziemann *et al.* (2009)
Mutation assay (*lac*I transgene) in brain tissue of Big Blue mice	1500 MHz	0, 0.67, or 2 W/kg	90 min/d, 5 d/wk, for 4 wk	None	–		Takahashi *et al.* (2002)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
Mutation frequency of the *lacZ* gene in cells from the spleen, liver, brain and testes of the offspring of *lacZ*- transgenic mice	2450 MHz (intermittent, 10 s on, 50 s off)	0.71 W/kg (average); 4.3 W/kg (for 10 s exposures)	Exposure *in utero* for 16 h/d on days 0–15 of gestation	None	–	Offspring was analysed at age 10 wk	Ono *et al.* (2004)
DNA microsatellite analysis with synthetic oligonucleotide probes in cells of brain and testis of Swiss albino mice	2450 MHz, CW	1.2 W/kg	2 h/d, for 120, 150, 200 d	None	+	Change in length of a microsatellite sequence	Sarkar *et al.* (1994)
DNA damage assessed by quantitative PCR (Q-PCR), alkaline- and pulsed-field electrophoresis in caudal epididymal spermatozoa of CD1 Swiss mice	900 MHz	0.09 W/kg	12 h/d, for 7 d	None	+	No effect on male germ-cell development; Q-PCR showed damage in mitochondrial genome and in nuclear β-globin locus	Aitken *et al.* (2005)
Somatic intrachromosomal recombination in spleen cells of pKZ1 transgenic mice	900 MHz, PW	4 W/kg	30 min/d for 1, 5, 25 d	None	–	Reduction in inversions below the spontaneous frequency in the group exposed for 25 d	Sykes *et al.* (2001)
Rat							
MN formation in peripheral-blood and bone-marrow cells of male Sprague-Dawley rats	2450 MHz, CW	12 W/kg	24 h	None	–		Vijayalaxmi *et al.* (2001a)
MN formation in peripheral blood cells of male Wistar rats	2450 MHz, CW	1 and 2 W/kg	2 h/d for up to 30 d	None	+	Only after 8 (not 2, 15, or 30) exposures of 2 h each	Trosic *et al.* (2002)
MN formation in PCEs in bone marrow and peripheral blood of Wistar rats	2450 MHz	Whole-body SAR, 1.25 W/kg	2 h/d, 7 d/wk, 30 d	None	+	Increased MN frequency in PCEs in bone marrow on day 15, and in the peripheral blood on day 8	Trosic & Busljeta (2006)
MN formation in bone-marrow cells of male and female Wistar rats	910 MHz	Peak SAR, 0.42 W/kg	2 h/d for 30 consecutive days	None	+		Demsia *et al.* (2004)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
MN formation in bone-marrow cells of male Wistar rats	2450 MHz, CW	1.25 W/kg	2 h/d for up to 30 days (total exposure 4, 16, 30 or 60 h)	None	+	Increase in PCE in bone marrow on day 15 (exposure, 30 h). Transient effect on proliferation and maturation of erythropoietic cells	Trosic *et al.* (2004); Busljeta *et al.* (2004)
MN formation in blood from adult pregnant Wistar rats	834 MHz, mobile-phone antenna, 26.8–40 V/m	0.55–1.23 W/kg	From day 1 of gestation, for 8.5 h/d, until birth of offspring	None	+	Significant increase of MN frequency in erythrocytes of newborn pups exposed *in utero*	Ferreira *et al.* (2006)
MN formation in blood of female Wistar rats	900 MHz, AM	0.3 and 0.9 W/kg	2 h/d, 5 d/wk, for 2 yr	Coexposure with MX in drinking-water	–	No increase in MN after coexposure to MX and RF radiation compared with MX [no group exposed to RF only]	Verschaeve *et al.* (2006)
MN formation in blood cells of Wistar rats	10 000 MHz 50 000 MHz	0.04 W/kg 0.0008 W/kg	2 h/d for 45 d	None	+ +	Also significant increase of ROS in serum	Kumar *et al.* (2010)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, PW or CW	0.6 and 1.2 W/kg	2 h	None	+	Significant and SAR-dependent increase in SB immediately and at 4 h after exposure to CW; only at 4 h after exposure to PW	Lai & Singh (1995)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, PW or CW	1.2 W/kg	2 h	None	+	Significant increase in SB at 4 h after exposure to either PW or CW	Lai & Singh (1996)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, PW	1.2 W/kg	2 h	Melatonin or *N*-tert-butyl-α-phenylnitrone (free-radical scavengers)	+	Significant increase in SB at 4 h after exposure. Treatment with radical scavengers before and after exposure to RF prevented/reversed induction of SB	Lai & Singh (1997)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
DNA breaks (SSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, CW	1.2 W/kg	2 h	None	–		Malyapa *et al.* (1998)
DNA breaks (SSB) measured with alkaline comet assay (with or without proteinase K) in brain cells of male Sprague-Dawley rats	2450 MHz, PW	1.2 W/kg	2 h	None	–		Lagroye *et al.* (2004a)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, CW, circular polarization	0.6 W/kg	2 h	None	+	Significant increase in SB at 4 h after exposure	Lai & Singh (2005)
DNA breaks (DSB) measured with pulsed-field electrophoresis. Changes in chromatin conformation detected with AVTD assay in brain cells from Wistar rats	915 MHz (GSM)	0.4 W/kg	2 h	None	–	Changes in gene expression were detected	Belyaev *et al.* (2006)
DNA breaks (SSB) measured with alkaline comet assay in brain cells of male and female Wistar rats	2450 MHz or 16 500 MHz	1.0 W/kg or 2.01 W/kg	2 h/d, for 35 d	None	+	DNA breakage was observed at both frequencies	Paulraj & Behari (2006)
DNA breaks (SSB) measured with alkaline comet assay in blood, liver and brain of female Wistar rats	900 MHz, AM	0.3 or 0.9 W/kg	2 h/d, 5 d/wk for 2 yr	Co-exposure with MX in drinking-water	–	No increase in SB after co-exposure to MX and RF radiation compared with MX [no group exposed to RF only]	Verschaeve *et al.* (2006)
DNA breaks (DSB) measured with neutral comet assay in brain of male Wistar rats	2450 MHz, from MW oven	0.11 W/kg (whole-body)	2 h/d, 35 d	None	+	Highly significant decrease in anti-oxidant enzymes and increase in catalase were also seen ($P < 0.006$)	Kesari *et al.* (2010)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
Rabbit							
Oxidative DNA damage (8-OHdG) in liver of pregnant and non-pregnant New Zealand White rabbits	1800 MHz (GSM-like)	NR	15 min/d for 1 wk (for pregnant rabbits: days 15–22 of gestation)	None	–	No difference in 8-OHdG/10^6dG between exposed and sham-exposed non-pregnant or pregnant rabbits, or between newborns exposed *in utero* and sham-exposed newborns	Tomruk *et al.* (2010)
Cow							
MN formation in erythrocytes of Latvian Brown cows living in the Skrunda radio-station area	154–162 MHz, PW	NR	Cows had been living in the area for at least 2 yr	None	+	Significant increase in MN compared with cows in a control area. Frequencies of MN were low in all cases	Balode (1996)

+, increase; –, no effect; AVTD, anomalous viscosity time-dependence; CW, continuous wave; d, day; DAMPS, Digital Advanced Mobile Phone System, DCS, Digital Cellular System; DSB, DNA double-strand breaks; GSM, Global System for Mobile Communications; h, hour; MED, minimal erythema dose; min, minute; MN, micronuclei; MW, microwave; MX, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone; NMT, Nordic Mobile Telephone; NR, not reported; PCE, polychromatic erythrocytes; PW, pulsed wave; s, second; SAR, specific absorption rate; SB, DNA strand breaks, SSB, DNA single-strand breaks; wk, week; yr, year

months and brain and liver samples were taken at the end of the study (24 months). The extent of DNA strand breaks in blood, liver and brain cells was determined by means of the alkaline comet assay; the frequency of micronuclei was measured in erythrocytes. Coexposure to MX and RF radiation did not significantly change the effects in blood, liver and brain cells compared with those seen with MX only [the Working Group noted that this study did not include a treatment group exposed to RF radiation only].

Induction of DNA double-strand breaks was measured by means of pulsed-field gel electrophoresis, and changes in chromatin conformation were assessed by use of the anomalous viscosity time-dependence (AVTD) assay in brain tissue of Fisher rats exposed to RF radiation at 915 MHz (GSM; SAR, 0.4 W/kg) for 2 hours. No effects of exposure to RF radiation were found. Analysis of gene-expression profiles in the cerebellum of exposed rats revealed changes in genes associated with neurotransmitter regulation, melatonin production and regulation of the blood–brain barrier (Belyaev *et al.*, 2006).

(iii) 1600 MHz

Timed-pregnant Fischer 344 rats were exposed from day 19 of gestation, and their nursing offspring until weaning at 3 weeks of age, to far-field RF radiation at 1600 MHz (iridium wireless-communication signal) for 2 hours per day, 7 days per week. The whole-body average SAR was 0.036–0.077 W/kg (0.10–0.22 W/kg in the brain). This first exposure was followed by long-term, head-only exposures of male and female offspring (starting at age 35 days) to a near-field 1600 MHz signal, with a SAR of 0.16 or 1.6 W/kg in the brain, for 2 hours per day, 5 days per week, for 2 years. The micronucleus frequency in polychromatic erythrocytes of the bone marrow was not significantly different between exposed, sham-exposed and cage-control rats (Vijayalaxmi *et al.*, 2003).

(iv) 2450 MHz

In several publications from the same laboratory it was reported that brain cells of male Sprague-Dawley rats exposed for 2 hours to low-intensity pulsed-wave or continuous-wave RF radiation at 2450 MHz (SAR, 0.6 or 1.2 W/kg) showed an increased number of DNA single- and double-strand breaks – measured by the neutral and alkaline comet assays – at 4 hours after exposure. The authors suggested that this could be due either to a direct effect on DNA or to an effect on DNA repair (Lai & Singh, 1995, 1996). In subsequent experiments, treatment of the rats with free-radical scavengers appeared to block this effect of RF exposure, suggesting that free radicals may be involved in RF-radiation-induced DNA damage in the rat brain (Lai & Singh, 1997).

Male Sprague-Dawley rats were exposed to continuous-wave RF radiation at 2450 MHz (SAR of 1.2 W/kg) for 2 hours, which did not cause a rise in the core body-temperature of the rats. One group of rats was killed by carbon dioxide (CO_2) asphyxia, another by decapitation. DNA breakage was assessed by means of the alkaline comet assay. No significant differences were observed in the comet length or the normalized comet moment of cells isolated from either the cerebral cortex or the hippocampus of irradiated rats and those from sham-exposed rats. This was independent of the method by which the rats were killed. However, there was more intrinsic DNA damage and more experiment-to-experiment variation in cells from the asphyxiated rats than from rats killed by decapitation. Therefore, the latter method appeared to be the most appropriate in this type of study (Malyapa *et al.*, 1998). [The Working Group noted that this study was not a valid replication of the Lai & Singh (1995) study, contrary to the authors' intention, but it provided independent evidence contrary to those results. The Working Group also noted that the increased number of DNA strand breaks after

exposure to RF radiation *in vivo* was particularly protocol-dependent, specifically with respect to the method of killing the animals and the treatment of tissue samples between exposure of the animals and analysis of the tissues.]

Vijayalaxmi *et al.* (2001a) found no evidence for the induction of micronuclei in peripheral-blood and bone-marrow cells of Wistar rats exposed continuously to continuous-wave RF radiation at 2450 MHz, with an average whole-body SAR of 12 W/kg, for 24 hours.

Lagroye *et al.* (2004a) investigated the induction of DNA damage in brain cells of Sprague-Dawley rats exposed to pulsed-wave RF radiation at 2450 MHz, with a SAR of 1.2 W/kg, for 2 hours. The rats were decapitated 4 hours after exposure. No DNA damage was detected in separate samples of the same brain-cell preparation from exposed rats, assessed by two variants of the alkaline comet assay.

Wistar rats were exposed to non-thermal RF radiation at 2450 MHz for 2 hours per day on 7 days per week, for up to 30 days. The power-density range was 5–10 mW/cm^2, which corresponded to an approximate SAR of 1–2 W/kg. Erythrocyte counts, haemoglobin concentrations and haematocrit values were significantly increased in peripheral blood on days 8 and 15, and anuclear cells and erythropoietic precursor cells in bone marrow were significantly decreased. The frequency of micronucleated cells in the bone marrow was significantly increased on day 15, not on days 2, 8, and 30 (Busljeta *et al.*, 2004).

Adult male Wistar rats were exposed to continuous-wave RF radiation at 2450 MHz for 2 hours per day, 7 days per week, for up to 30 days. The power-density range was 5–10 mW/cm^2, which corresponded to an approximate SAR of 1–2 W/kg. The frequency of micronuclei in polychromatic erythrocytes was significantly increased in the group that had received 8 irradiation treatments of 2 hours each, but not in the groups that received 2, 15 or 30 treatments, in comparison with the sham-exposed group. These results would be in line with an adaptive or recovery mechanism that was triggered in this experimental model during treatment (Trosic *et al.*, 2002, 2004). Similar results were presented in a later publication (Trosic & Busljeta, 2006).

Paulraj & Behari (2006) reported a significantly increased ($P < 0.001$) level of DNA breakage – measured by means of the alkaline comet assay – in brain cells of rats exposed to RF radiation at 2450 MHz or 16.5 GHz (SAR, 1.0 or 2.01 W/kg) for 2 hours per day, for 35 days.

Wistar rats were exposed to RF radiation at 2450 MHz (power density, 0.34 mW/cm^2) for 2 hours per day, for 35 days. The whole-body SAR was estimated to be 0.11 W/kg. After exposure, rats were killed and whole-brain tissue was dissected and used for analysis of DNA double-strand breaks by means of the neutral comet assay. A significant increase was observed in various comet parameters in exposed brain cells compared with controls. Statistically significant changes were also observed in the levels of different antioxidant enzymes, *i.e.* a decrease in glutathione peroxidase, superoxide dismutase and histone kinase, and an increase in catalase (Kesari *et al.*, 2010).

(v) 10–50 GHz

Wistar rats were exposed continuously to RF radiation at 10 GHz or 50 GHz (SAR, 0.014 W/kg and 0.0008 W/kg, respectively) for 2 hours per day, for 45 days. In both cases, significant increases ($P < 0.05$) in the frequency of micronuclei – deduced from a reduced polychromatic/normochromatic erythrocyte ratio – and in concentrations of reactive oxygen species (ROS) were found in blood cells and serum, respectively (Kumar *et al.*, 2010).

(d) Rabbit

A study was performed with non-pregnant and pregnant New Zealand White rabbits. The rabbits were exposed (whole-body) to 1800 MHz RF radiation (GSM) for 15 minutes per day,

for 1 week. For the pregnant rats, this exposure period was between day 15 and day 22 of gestation. Control groups of non-pregnant and pregnant rabbits were sham-exposed. No difference was found in the level of 8-hydroxy-2′-deoxyguanosine (an indicator of oxidative DNA damage; expressed as 8-OHdG/10^6 dG) in DNA from liver tissue of exposed and sham-exposed rabbits (pregnant or non-pregnant). Changes in malondialdehyde concentration and ferrous oxidation in xylenol orange in the liver of exposed non-pregnant and pregnant rabbits indicated an effect on lipid peroxidation. In pups exposed *in utero*, a reduction in ferrous oxidation in xylenol orange was seen in the liver, but no change was observed in malondialdehyde concentration. These results supported the notion that 1800 MHz GSM-like RF radiation may induce oxidative stress in exposed tissues (Tomruk *et al.*, 2010).

(e) Cow

Blood samples were obtained from 67 female Latvian Brown cows living on a farm in the vicinity of the Skrunda radio-location station (Latvia), and from 100 cows in a control area, which was selected on the basis of the similarity to the exposed area with regards to many factors except exposure. Frequencies of micronuclei were scored in the erythrocytes and found to be low but statistically significantly increased in the exposed cows compared with those in the controls (0.6/1000 cells compared with 0.1/1000 cells; $P < 0.01$) (Balode, 1996).

4.1.3 Experimental systems: in vitro

(a) Humans: peripheral blood lymphocytes

The most widely used cell type for investigations *in vitro* is the peripheral blood lymphocyte. Some details on the exposure conditions to RF radiation and a short conclusion of the publications discussed below are presented in Table 4.4.

(i) Studies with a single end-point

DNA-damage induction and repair

The effects of exposure to RF radiation at frequencies ranging from approximately 800 to 8000 MHz were examined by several investigators, who reported no significant effect on induction of DNA strand breaks (Baohong *et al.*, 2005, 2007; Chemeris *et al.*, 2006; Sannino *et al.*, 2006).

Vijayalaxmi *et al.* (2000) assessed DNA strand breaks in human lymphocytes and also the capacity of these cells to repair such damage after exposure to RF radiation at 2450 MHz, and observed no effect on either parameter. Zhijian *et al.* (2009) also reported no effect of exposure to RF radiation at 1800 MHz, not only on induction of DNA strand breaks but also on the repair kinetics of X-irradiation-induced DNA strand breaks. Tiwari *et al.* (2008) exposed human lymphocytes to RF radiation at 835 MHz (SAR, 1.17 W/kg) and subsequently incubated the cells in the presence of aphidicolin (APC; an inhibitor of DNA repair) at a dose of 0.02 or 2 µg/ml. There was no effect on DNA strand breakage from exposure to RF radiation alone. APC (2 µg/ml) and combinations of RF radiation with APC (0.02 and 2 µg/ml) enhanced the number of DNA strand breaks; this damage is repairable (see Section 4.1.3c).

Chromosomal aberrations

Maes *et al.* (1995) found an increase in the frequency of chromosomal aberrations in the form of dicentrics and acentric fragments in human lymphocytes exposed to pulsed-wave RF radiation at 954 MHz, while using a cooled box to maintain the temperature at 17 ± 1 °C. Manti *et al.* (2008) carried out FISH analysis with molecular probes specific for whole chromosomes 1 and 2 in lymphocytes from four donors. The cells were exposed to RF radiation at 1950 MHz (UMTS, Universal Mobile Telecommunications System) at SAR 0.5 or 2.0 W/kg, for 24 hours. There was no effect on the fraction of aberrant cells at a

Table 4.4 Genetic and related effects in human peripheral blood lymphocytes exposed to radiofrequency radiation *in vitro*

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Aneuploidy	830 MHz, CW	2.0–8.2 W/kg	72 h	+ (chromosome 17)	Temperature kept at 33.5–37.5 °C. In control without RF, no aneuploidy was seen up to 38.5 °C	Mashevich *et al.* (2003)
Aneuploidy	100 GHz, CW	0.31 mW/cm^2	1–24 h	+ (chromosomes 11, 17) – (chromosomes 1, 10)	Direct effect questionable. High values in control cells.	Korenstein-Ilan *et al.* (2008)
Aneuploidy	800 MHz, CW	2.9, 4.1 W/kg	24 h	+ (chromosomes 11, 17) at SAR of 2.9 W/kg + (chromosomes 1, 10) at SAR of 4 W/kg	High values in control cells. In control without RF, no aneuploidy was seen up to 40 °C	Mazor *et al.* (2008)
Chromosomal aberration	7700 MHz, CW	0.5, 10, 30 mW/cm^2	10, 30, 60 min	+	Abberations increased at 10 and 30 mW/cm^2 at all time-points	Garaj-Vrhovac *et al.* (1992)
Chromosomal aberration	2450 MHz, PW	75 W/kg	30 min, 2 h	+	MW output was adjusted with a thermistor to keep cells at 36.1 °C	Maes *et al.* (1993)
Chromosomal aberration	954 MHz, PW; GSM	1.5 W/kg	2 h	±	Questionable dosimetry (pylon from GSM base-station connected to indoor antenna); no statistics provided	Maes *et al.* (1995)
Chromosomal aberration	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	–		Eberle *et al.* (1996)
Chromosomal aberration	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h	–		Maes *et al.* (1997)
Chromosomal aberration	2450 MHz, CW	12.5 W/kg	90 min or 3 × 30 min	–		Vijayalaxmi *et al.* (1997b)
Chromosomal aberration	455.7 MHz, PW	6.5 W/kg	2 h	–	Cells were placed 5 cm from a car phone	Maes *et al.* (2000)
Chromosomal aberration	900 MHz, PW; CDMA	0.4–10 W/kg	2 h	–		Maes *et al.* (2001)
Chromosomal aberration	835.62 MHz, CW; FDMA	4.4, 5.0 W/kg	24 h	–		Vijayalaxmi *et al.* (2001a)
Chromosomal aberration	847.74 MHz, CW; CDMA	4.9, 5.5 W/kg	24 h	–		Vijayalaxmi *et al.* (2001b)
Chromosomal aberration	2500 MHz 10 500 MHz	627 W/kg 0.25 W/kg	40 s 5 min	– –	MW oven at 3 W	Figueiredo *et al.* (2004)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Chromosomal aberration	900 MHz, PW; GSM	0.3, 1 W/kg	2 h	–		Zeni *et al.* (2005)
Chromosomal aberration	935 MHz, PW; GSM	1, 2 W/kg	24 h	–		Stronati *et al.* (2006)
Chromosomal aberration	2450, 8200 MHz, PW	2.1, 21 W/kg	2 h	–		Vijayalaxmi *et al.* (2006)
Chromosomal aberration	1950 MHz, PW; UMTS	0.5, 2 W/kg	24 h	– at SAR of 0.5 W/kg + at SAR of 2 W/kg	Frequency of aberrations/cell was increased at higher SAR; FISH technique was used	Manti *et al.* (2008)
Chromosomal aberration	18 000 MHz, CW 16 500 MHz, PW	1 mW/cm^2 10 mW/cm^2	53 h	–		Hansteen *et al.* (2009a)
Chromosomal aberration	2300 MHz, CW, PW	1 mW/cm^2	53 h	–		Hansteen *et al.* (2009b)
Micronucleus formation	7700 MHz, CW	0.5, 10, 30 mW/cm^2	10, 30, 60 min	+	MN frequency increased at 30 mW/cm^2, after 30 and 60 min of exposure	Garaj-Vrhovac *et al.* (1992)
Micronucleus formation	2450 MHz, PW	75 W/kg	30 min, 2 h	+	MW output was adjusted with a thermistor to keep cells at 36.1 °C	Maes *et al.* (1993)
Micronucleus formation	9000 MHz, CW, PW	90 W/kg	10 min	+ with PW – with CW	Temperature during exposure was 30–35 °C. Control cultures were kept at 37 °C	d'Ambrosio *et al.* (1995)
Micronucleus formation	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	–		Eberle *et al.* (1996)
Micronucleus formation	2450 MHz, CW	12.5 W/kg	3 × 30 min	–		Vijayalaxmi *et al.* (1997b)
Micronucleus formation	2450, 7700 MHz, CW	10, 20, 30 mW/cm^2	15, 30, 60 min	+	Experiment carried out at 20–22 °C. Temperature-control measurements were made in water	Zotti-Martelli *et al.* (2000)
Micronucleus formation	835.62 MHz, CW; FDMA	4.4, 5.0 W/kg	24 h	–		Vijayalaxmi *et al.* (2001a)
Micronucleus formation	847.74 MHz, CW; CDMA	4.9, 5.5 W/kg	24 h	–		Vijayalaxmi *et al.* (2001b)
Micronucleus formation	1748 MHz, CW, PW; GSM	5 W/kg	15 min	+ with PW – with CW	Temperature during exposure was 30–35 °C. Control cultures were kept at 37 °C	d'Ambrosio *et al.* (2002)
Micronucleus formation	1900 MHz, CW, PW	0.1–10 W/kg	2 h	–		McNamee *et al.* (2002a)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Micronucleus formation	2450 MHz, PW	5 mW/cm^2	2 h	–		Zhang *et al.* (2002)
Micronucleus formation	837, 1909 MHz, CW, PW; CDMA, TDMA	1.0, 2.5, 5.0, 10.0 W/kg	3 h, 24 h	+ after 24 h,at SARs of 5 or 10 W/kg	Some exposures were from mobile telephones. Temperature variations were ± 0.3 °C and ± 0.5 °C at 3 h and 24 h, respectively. EMS was included as a positive control	Tice *et al.* (2002)
Micronucleus formation	1900 MHz, CW, PW	0.1–10 W/kg	24 h	–		McNamee *et al.* (2003)
Micronucleus formation	120, 130 GHz PW	1 and 0.6 mW average power	20 min	–		Scarfi *et al.* (2003)
Micronucleus formation	900/925 MHz, CW, PW(i); GSM	1.6 W/kg 0.2 W/kg	14 × (6 min on, 3 h off) at 1.6 W/kg; 1 h/d for 3 d at 0.2 W/kg	–		Zeni *et al.* (2003)
Micronucleus formation	1800 MHz, CW	5, 10, 20 mW/cm^2	1, 2, 3 h	+	Large variation between individuals and repeat experiments	Zotti-Martelli *et al.* (2005)
Micronucleus formation	900 MHz, PW; GSM	0.1–10 W/kg	24 h	–	Concordant results between two research groups in interlaboratory study	Scarfi *et al.* (2006)
Micronucleus formation	935 MHz, PW; GSM	1, 2 W/kg	24 h	–		Stronati *et al.* (2006)
Micronucleus formation	2450, 8200 MHz, PW	2.1, 21 W/kg	2 h	–		Vijayalaxmi *et al.* (2006)
Micronucleus formation	1950 MHz, PW (c, i); UMTS	0.05–2 W/kg	4–48 h	–	Controversial data	Schwarz *et al.* (2008)
Micronucleus formation	1950 MHz, PW (c, i); UMTS	2.2 W/kg	24–68 h	–		Zeni *et al.* (2008)
Micronucleus formation	900 MHz, PW; GSM	1.25 W/kg	20 h	–	No effect of RF radiation alone. Reduction of MMC-induced micronucleus frequency. Data indicative of an adaptive response	Sannino *et al.* (2009a)
Sister-chromatid exchange	2450 MHz, PW	75 W/kg	30 min, 2 h	–	MW output was adjusted with a thermistor to keep cells at 36.1 °C	Maes *et al.* (1993)
Sister-chromatid exchange	954 MHz, PW; GSM	1.5 W/kg	2 h	–		Maes *et al.* (1996)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Sister-chromatid exchange	380, 900, 1800 MHz, PW; TETRA, DCS, GSM	0.08–1.7 W/kg	72 h	–		Antonopoulos *et al.* (1997)
Sister-chromatid exchange	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	–		Eberle *et al.* (1996)
Sister-chromatid exchange	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h	–		Maes *et al.* (1997)
Sister-chromatid exchange	455.7 MHz, PW; car phone	6.5 W/kg	2 h	–		Maes *et al.* (2000)
Sister-chromatid exchange	900 MHz, PW; GSM	0.4–10 W/kg	2 h	–		Maes *et al.* (2001)
Sister-chromatid exchange	900 MHz, PW; GSM	0.3, 1 W/kg	2 h	–		Zeni *et al.* (2005)
Sister-chromatid exchange	400–900 MHz, PW	-	-	–		Maes et al. (2006)
Sister-chromatid exchange	935 MHz, PW; GSM	1, 2 W/kg	24 h	–		Stronati *et al.* (2006)
DNA single- and double-strand breaks	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h	–		Maes *et al.* (1997)
DNA single- and double-strand breaks	2450 MHz, PW	2.1 W/kg	2 h	–	No effect, immediately or 4 h after exposure	Vijayalaxmi *et al.* (2000)
DNA single- and double-strand breaks	1900 MHz, CW, PW	0.1–10 W/kg	2 h	–		McNamee *et al.* (2002a)
DNA single- and double-strand breaks	2450 MHz, PW	5 mW/cm^2	2 h	–		Zhang *et al.* (2002)
DNA single- and double-strand breaks	837, 1909 MHz, CW, PW; CDM, TDM	1.0, 2.5, 5.0, 10.0 W/kg	3 h, 24 h	–	Some exposures were from mobile telephones. Temperature variations were ± 0.3 °C and ± 0.5 °C at 3 h and 24 h, respectively. EMS was included as a positive control.	Tice *et al.* (2002)
DNA single- and double-strand breaks	1900 MHz, CW, PW	0.1–10 W/kg	24 h	–		McNamee *et al.* (2003)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	1800 MHz, PW; GSM	3 W/kg	2 h	–		Baohong *et al.* (2005)
DNA single- and double-strand breaks	900 MHz, PW; GSM	0.3, 1 W/kg	2 h	–		Zeni *et al.* (2005)
DNA single- and double-strand breaks	8800 MHz, PW	1.6 kW/kg	40 min	–		Chemeris *et al.* (2006)
DNA single- and double-strand breaks	1950 MHz, PW; UMTS	0.5, 2 W/kg	24 h	–		Sannino *et al.* (2006)
DNA single- and double-strand breaks	935 MHz, PW; GSM	1, 2 W/kg	24 h	–		Stronati *et al.* (2006)
DNA single- and double-strand breaks	1800 MHz, PW; GSM	3 W/kg	1.5, 4 h	–		Baohong *et al.* (2007)
DNA single- and double-strand breaks	120 000, 130 000 MHz, PW; THz	0.2–2 W/kg	20 min	–		Zeni *et al.* (2007a)
DNA single- and double-strand breaks	1950 MHz, PW(c, i); UMTS	0.05–2 W/kg	4–48 h	–	Controversial data	Schwarz *et al.* (2008)
DNA single- and double-strand breaks	835 MHz, PW; CDMA	1.17 W/kg	1 h	–	RF radiation induced repairable DNA damage in the presence of aphidicolin	Tiwari *et al.* (2008)
DNA single- and double-strand breaks	1950 MHz, PW(c, i); UMTS	2 W/kg	24–68 h	–		Zeni *et al.* (2008)
DNA single- and double-strand breaks	1800 MHz, PW(i); GSM	2 W/kg	24 h	–	No effect of RF radiation on repair of X-ray-induced DNA damage	Zhijian *et al.* (2009)
Mutation at *HPRT* locus	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	–		Eberle *et al.* (1996)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Foci	915 MHz, PW; GSM	37 mW/kg	2 h	+	Decrease in 53BP1-foci (measured by immuno-staining); enhanced chromatin condensation (measured by AVTD)	Belyaev *et al.* (2005)
Foci	905, 915 MHz, PW; GSM	37 mW/kg	1 h	+ at 915 MHz – at 905 MHz	Decrease in 53BP1- and γ-H2AX-foci (measured by immunostaining) and enhanced chromatin condensation (measured by AVTD)	Markovà *et al.* (2005)
Foci	905, 915, 1947 MHz, PW; GSM, UMTS	0.015–0.145 W/kg	1 h	+ at 915 MHz – at 905 MHz + t 1947 MHz	Decrease in 53BP1- and γ-H2AX-foci (measured by immunostaining) and enhanced chromatin condensation (measured by AVTD). Strongest effect at 1947 MHz	Belyaev *et al.* (2009)

+, increase; ±, equivocal; – , no effect; APC, aphidicholin (inhibitor of DNA repair); AVTD, anomalous viscosity time-dependence; (c, i): continuous or intermittent exposure; CA, chromosomal aberration; CDMA, code-division multiple access; CW, continuous wave; d, day; DCS, Digital Communication System; EMS, ethylmethane sulfonate; FDMA, frequency-division multiple access; FISH, fluorescence *in situ* hybridization; GSM, Global System for Mobile Communication; h, hour; HPRT, hypoxanthine(guanine)phosphoribosyl transferase; min, minute; MMC, mitomycin C; MW, microwave; PW, pulsed wave; s, second; TDMA, time-division multiple access; TETRA, Trans European Trunked Radio; THz; teraHertz; UMTS, Universal Mobile Telecommunication System

SAR of 0.5 W/kg, while there was a small but statistically significant increase in the frequency of aberrations per cell at 2 W/kg. Figueiredo *et al.* (2004) and Hansteen *et al.* (2009a, b) carried out conventional analyses of chromosomal aberrations on Giemsa-stained slides prepared with lymphocytes exposed to RF radiation at 1800–10 500 MHz, and observed no effect.

Micronucleus formation

Zotti-Martelli *et al.* (2000) exposed whole blood from two volunteers to continuous-wave RF radiation at 2450 MHz or 7700 MHz, with power densities of 10, 20 and 30 mW/cm^2 for 15, 30, and 60 minutes, and reported an increased micronucleus frequency in exposed cells at 30 mW/cm^2. In a subsequent study, Zotti-Martelli *et al.* (2005) observed an increase in the frequency of micronuclei in lymphocytes from nine different donors after exposure to RF radiation at 1800 MHz. This experiment was repeated after 3 months; there was significant variation between experiments. [The Working Group noted that temperature variation in the first study was not measured in blood samples during exposure, and the increased frequency of micronucleus formation may have been related to heating of the blood samples. Also, there were discrepancies between the data on micronuclei given in the text, figures, and tables]. d'Ambrosio *et al.* (1995, 2002) reported an increase in the formation of micronuclei in lymphocytes exposed to pulsed-wave RF radiation at 1748 MHz or 9000 MHz for 15 and 10 minutes, respectively, while no such increase was observed in cells exposed to continuous-wave RF at the same frequencies. Zeni *et al.* (2003) observed no significant effect on micronucleus formation in lymphocytes exposed to continuous or pulsed-wave RF radiation at 900 MHz (GSM). Scarfi *et al.* (2003) reported no micronucleus induction in lymphocytes exposed to continuous-wave RF radiation at 120–130 GHz. Sannino *et al.* (2009a) reported that a 20-hour pre-exposure of peripheral blood lymphocytes in the S-phase of the cell cycle to pulsed-wave RF radiation at 900 MHz decreased the micronucleus frequency induced by mitomycin C (MMC), suggesting the existence of an adaptive response (see Table 4.4 for details).

Sister-chromatid exchange (SCE)

Maes *et al.* (1996) did not find an effect on SCE in lymphocytes exposed to pulsed-wave RF radiation at 954 MHz, with a SAR of 1.5 W/kg, for 2 hours. Likewise, Antonopoulos *et al.* (1997) did not find an effect on SCE in lymphocytes exposed to RF radiation at 380–1800 MHz, with a SAR of 0.08–1.7 W/kg, for 72 hours.

Phosphorylation of histone protein H2AX and TP53-binding protein 53BP1

Over the past decade, several studies have demonstrated that two cellular check-point proteins, H2AX and TP53-binding protein 53BP1 are rapidly phosphorylated after induction of DNA damage in the form of double-strand breaks. These proteins then congregate to provide a scaffold structure to the repair sites (Paull *et al.*, 2000; Schultz *et al.*, 2000; DiTullio *et al.*, 2002; Fernandez-Capetillo *et al.*, 2002, 2004; Sedelnikova *et al.*, 2002; Ismail *et al.*, 2007). By use of specific antibodies with fluorescent tags, γ-H2AX – the phosphorylated form of H2AX – and 53BP1 can be visualized as discrete foci, which can be counted directly with a fluorescence microscope.

The AVTD assay is used to detect stress-induced changes in chromatin conformation. Shckorbatov *et al.* (1998, 2009) and Sarimov *et al.* (2004) have reported changes in chromatin condensation in human lymphocytes exposed to RF radiation at 42.2 GHz, 35 GHz or 895–915 MHz, respectively, which prevented access of proteins involved in repair of DNA double-strand breaks. Belyaev *et al.* (2005) exposed human lymphocytes for 2 hours to pulsed-wave RF radiation at 915 MHz (GSM), with a SAR of 37 mW/kg, and reported significant

effects on chromatin condensation and a distinct reduction in the number of 53BP1-foci in samples from all individuals; these results were similar to those found after heat-shock treatment. The overall data suggested a reduced accessibility of 53BP1 to repair DNA double-strand breaks due to chromatin condensation. Markovà *et al.* (2005) exposed human lymphocytes to pulsed-wave RF radiation at 905 MHz or 915 MHz (GSM), with a SAR of 37 mW/kg, for 1 hour. Chromatin condensation and decreased numbers of 53BP1- and γ-H2AX-foci were observed in cells after exposure at 915 MHz, but not at 905 MHz. The response was similar in healthy subjects and in subjects hypersensitive to RF radiation. Belyaev *et al.* (2009) exposed lymphocytes to pulsed-wave RF radiation at 905 MHz or 915 MHz (GSM), or 1947 MHz (UMTS), with a SAR of 15–145 mW/kg, for 1 hour. Chromatin condensation and reduction in numbers of 53BP1- and γ-H2AX-foci were much more pronounced in cells after exposure at 1947 MHz than at 915 MHz; there were no such effects after exposure at 905 MHz. The decrease in number of foci persisted for up to 72 hours after exposure, suggesting that not only the formation of double-strand breaks was affected, but also their repair. Markovà *et al.* (2010) used VH10 primary fibroblasts established from human foreskin and mesenchymal stem cells isolated from adipose tissue of two healthy persons. These cells were exposed to pulsed-wave RF radiation at 905 MHz or 915 MHz (GSM; SAR, 37 mW/kg), or at 1947 MHz (UMTS; SAR, 39 mW/kg), as a single exposure for 1, 2 or 3 hours, or as repeated exposures for 1 hour per day, 5 days per week, for 2 weeks. The decrease in the number of 53BP1-foci was more pronounced in stem cells than in foreskin fibroblasts, and the stem cells did not adapt to long-term exposure to RF radiation.

Aneuploidy

Peripheral blood lymphocytes from five individuals were stimulated with phytohaemagglutinin (PHA) and exposed for 72 hours to continuous-wave RF radiation at 830 MHz (SAR, 1.6–8.8 W/kg), in an incubator set at temperatures between 33.5 °C (at the highest SAR value) and 37.5 °C. The incidence of aneuploidy of chromosome 17 was determined by use of a probe for α-satellite DNA repeat-sequences present in its centromeric region. The data indicated a linear and SAR-dependent increase in aneuploidy in cells exposed to RF radiation at SAR 2.0–8.2 W/kg (6–9%) compared with control cells (4–5%). Control experiments without RF radiation were conducted at 34.5–41 °C, showing no change in aneuploidy at temperatures up to 38.5 °C. This indicates that the effect of RF radiation was produced via a non-thermal pathway (Mashevich *et al.*, 2003).

Peripheral blood lymphocytes from nine donors were stimulated with PHA for 1–6 hours, then exposed to continuous-wave RF radiation at 100 GHz (power density, 0.031 mW/cm^2) for 1, 2 or 24 hours in an incubator in which CO_2 levels were not controlled. After exposure, the cells were incubated for a total culture period of 69–72 hours, with CO_2 levels at 5%. The cells were harvested and changes in chromosomes 1, 10, 11 and 17 were analysed by means of the FISH technique. For chromosomes 11 and 17, a 30% increase in aneuploidy was found after exposure for 2 or 24 hours, while chromosomes 1 and 10 were not affected. Asynchronous replication of centromeres 1, 11, and 17 was increased by 40% after 2 hours of exposure, while that of all four centromeres had increased by 50% after 24 hours of exposure. During the experiments, fibre-optic sensors were used to measure differences in temperature between exposed and sham-exposed samples; the difference never exceeded 0.3 °C (Korenstein-Ilan *et al.*, 2008).

Mazor *et al.* (2008) exposed PHA-stimulated lymphocytes from 10 individuals to continuous-wave RF radiation at 800 MHz (SAR, 2.9 or 4.1 W/kg) for 72 hours, with the incubator set at 33.5 °C to maintain the sample temperature at 36–37 °C, in particular at the high SAR value.

Aneuploidy was scored for chromosomes 1, 10, 11, and 17 by use of the FISH technique. An increased frequency of cells aneuploid for chromosomes 11 and 17 was observed at the lower SAR of 2.9 W/kg, and for chromosomes 1 and 10 at the higher SAR of 4.1 W/kg. Multisomy (chromosomal gain) was the primary contributor to the increase in aneuploidy. Control experiments – without exposure to RF radiation – were conducted in the temperature range 33.5–41 °C; there was no change in aneuploidy.

Spindle disturbance (experiments with human-hamster hybrid cells)

The well established human–hamster hybrid (A_L) cell line, containing a single copy of human chromosome 11, was exposed to pulsed-wave RF radiation at 835 MHz, with increasing electric field strengths from 5 to 90 V/m, for 30 minutes (Schmid & Schrader, 2007). The results indicated a field strength-dependent increase in the frequency of spindle disturbances during anaphase/telophase of cell division. [The Working Group noted the absence of negative and positive controls.] Schrader *et al.* (2008) reported similar increases in spindle disturbances in A_L cells exposed for 30 minutes or 2 hours to RF radiation at 835 MHz (90 V/m) compared with non-exposed controls. Schrader *et al.* (2011) exposed A_L cells to RF radiation at 900 MHz (amplitude-modulated and unmodulated), at electric field strengths of 45 or 90 V/m, and with a SAR of 11.5 W/kg, for 30 minutes. The experiments were conducted with separate electric (E field) and magnetic (H field) components of RF radiation, at 20–22 °C. A significant increase in the frequency of spindle disturbances was observed in cells exposed to the E component, while no effect was seen in cells exposed to the H component (compared with non-exposed control cells). Hintzsche *et al.* (2011) also reported an increase in spindle disturbance during the anaphase/telophase of cell division in the same A_L cell line exposed to continuous-wave RF radiation at 106 GHz (power densities, 0.043–4.3 mW/cm^2) for 30 minutes.

(ii) Studies with two or more end-points

Tice *et al.* (2002) reported a significant and reproducible increase in micronucleus formation in human lymphocytes exposed for 24 hours to RF radiation at 837 or 1909.8 MHz, with an average SAR of 5.0 or 10.0 W/kg. There was no increase in the number of DNA strand breaks in leukocytes, as measured with the alkaline comet assay. McNamee *et al.* (2002a, 2003) reported no effects on DNA strand-break induction or micronucleus formation in cells exposed to continuous- or pulsed-wave RF radiation at 1900 MHz, with SARs of up to 10 W/kg, for 2 or 24 hours. Zhang *et al.* (2002) observed no induction of DNA strand breaks or formation of micronuclei in human lymphocytes exposed to pulsed-wave RF radiation at 2450 MHz compared with controls. Zeni *et al.* (2008) reported no increase in DNA strand breaks or micronucleus formation in human lymphocytes exposed to intermittent (6 minutes on, 2 hours off) RF radiation at 1900 MHz (SAR, 2.2 W/kg) for 24–68 hours. Likewise, Schwarz *et al.* (2008), reported no increase in DNA strand-break induction or micronucleus formation in PHA-stimulated or non-stimulated human lymphocytes exposed for 16 hours to intermittent (5 minutes on, 10 minutes off) RF radiation at 1950 MHz (SAR, 0.1 W/kg).

Garaj-Vrhovac *et al.* (1992) reported significantly increased frequencies of chromosomal aberrations and micronuclei in human peripheral blood lymphocytes exposed for up to 60 minutes to continuous-wave RF radiation at 7700 MHz, with power densities up to 30 mW/cm^2.

In a series of studies from one laboratory, no increase in the frequency of chromosomal aberrations or micronuclei was reported in human lymphocytes exposed to RF radiation at 2450 MHz for 90 minutes, to continuous-wave RF radiation at 835 or 847 MHz for 24 hours, or

to RF radiation at 2450 or 8200 MHz for 2 hours (Vijayalaxmi *et al.*, 1997b, 2001b, c, 2006).

Maes *et al.* (1993) found a time-dependent increase in the frequencies of chromosomal aberrations and micronuclei in peripheral blood lymphocytes exposed to pulsed-wave RF radiation at 2450 MHz (SAR, 75 W/kg) for 30 or 120 minutes. Both effects were statistically significant for the exposure of 120 minutes. No induction of SCE was found. In this study, the microwave output was adjusted by use of a thermistor thermometer to maintain the temperature of the cells at 36.1 °C. In subsequent experiments, Maes *et al.* (2000, 2001) examined human lymphocytes exposed to pulsed-wave RF radiation at 455.7 MHz (SAR, 6.5 W/kg) or 900 MHz (SAR, 0.4–10 W/kg) for 2 hours; no increase in chromosomal aberrations or SCE was observed.

Stronati *et al.* (2006) did not report significant changes in DNA strand-break induction, chromosomal aberrations, micronucleus formation or SCE in blood cells exposed to pulsed-wave RF radiation at 935 MHz (SAR, 1 or 2 W/kg). Eberle *et al.* (1996) measured chromosomal aberrations, micronucleus formation, SCE, and mutations at the *HPRT* locus in human lymphocytes exposed to RF radiation at 440, 900, or 1800 MHz (SAR, 1.5 W/kg). Exposure times varied (39, 50, 70 hours), depending on the experiment. No significant effects were observed for any of these end-points in RF-exposed cells compared with controls.

(b) Humans: other primary and continuously growing cultured cells

Some details on the exposure conditions to RF radiation and a short conclusion for each publication are presented in Table 4.5.

(i) Amniotic cells

Human amniotic cells were exposed to RF radiation at 900 MHz (GSM; SAR, 0.25 W/kg) for 24 hours. Chromosomes were stained by use of the R-banding method and examined to determine the incidence of structural and numerical aberrations. Exposure to RF radiation had no effect (Bourthoumieu *et al.*, 2010). [The Working Group noted that R-banding is not recommended for analysis of chromosomal aberrations.] In a subsequent study by the same authors, amniotic cells were collected during amniocentesis from three separate donors. The cells were cultured for 15 days before being exposed to RF radiation at 900 MHz (GSM, pulsed-wave; pulse duration, 0.577 ms; pulse-repetition rate, 217 Hz; SAR, 0.25, 1, 2 or 4 W/kg) for 24 hours in a wire-patch cell at exposure temperatures of 36.3 ± 0.4 °C, 37.0 ± 0.2 °C, 37.5 ± 0.4 °C and 39.7 ± 0.8 °C, respectively, for the four SAR levels. The cells were processed for analysis by two-colour FISH with centromeric α-satellite repetitive probes for chromosomes 11 and 17 in interphase cells. No significant differences were observed between exposed and sham-exposed cells in the percentages of monosomic, trisomic cells or the total number of cells aneuploid for chromosomes 11 or 17 (Bourthoumieu *et al.*, 2011).

(ii) Glioblastoma and neuroblastoma cells

No effects on DNA strand-break induction were observed in human U87MG glioblastoma cells exposed for up to 24 hours to continuous-wave or pulsed-wave RF radiation at 835, 847, or 2450 MHz (SAR, 0.6 W/kg at 835/847 MHz, and 0.7 or 1.9 W/kg at 2450 MHz) (Malyapa *et al.* (1997a, b).

Miyakoshi *et al.* (2002) did not find an effect on DNA strand-break induction in human MO54 glial cells – derived from a patient with a brain tumour – exposed to RF radiation at 2450 MHz (average SAR, 50 or 100 W/kg) for 2 hours. Likewise, Sakuma *et al.* (2006) reported no effect on DNA strand-break induction in human A172 glioblastoma cells exposed to pulsed-wave RF radiation at 2142.5 MHz (SAR, up to 800 mW/kg) for 2 or 24 hours, and Luukkonen *et al.* (2009, 2010) found no effects on DNA strand-break induction in cultured human SH-SY5Y

Table 4.5 Genetic and related effects in human cells (other than lymphocytes) exposed to radiofrequency radiation *in vitro*

End-point	Cells	Frequency	SAR or power density	Duration	Results	Comments	Reference
Aneuploidy	HAC	900 MHz, PW; GSM	0.25, 1, 2, 4 W/kg	24 h	–	Chromosomes 11 and 17 were included in this study	Bourthoumieu *et al.* (2011)
Chromosomal aberration	HAC	900 MHz, PW; GSM	0.25 W/kg	24 h	–		Bourthoumieu *et al.* (2010)
Micronucleus formation	BUC	PW; mobile phone	NR	1 h/d for 2.3 yr	+		Yadav & Sharma (2008)
Micronucleus formation	BUC	PW; mobile phone	NR	3 h/wk for 5–10 yr	–		Hintzsche & Stopper (2010)
Micronucleus formation	HSF	1800 MHz, CW, PW(i); GSM	2 W/kg	1, 4, 24 h	–	Replication study. Previous results not confirmed.	Speit *et al.* (2007)
Micronucleus formation	SHF	1950 MHz, PW(c-i); UMTS	0.05–2 W/kg	4–48 h	+ after 12 h exposure	Controversial data	Schwarz *et al.* (2008)
Micronucleus formation	SHF	900 MHz, PW; GSM	1 W/kg	24 h	–		Sannino *et al.* (2009b)
DNA single- and double-strand breaks	GLB	2450 MHz, CW	0.7 W/kg	2–24 h	–		Malyapa *et al.* (1997a)
DNA single- and double-strand breaks	GLB	835, 847 MHz, CW, PW; FMCW, CDMA	0.6 W/kg	2–24 h	–		Malyapa *et al.* (1997b)
DNA single- and double-strand breaks	GLB	2450 MHz	13–100 W/kg	2 h	–		Miyakoshi *et al.* (2002)
DNA single- and double-strand breaks	GLB	2000 MHz, PW; CW, IMT	0.08, 0.25, 0.80 W/kg	2 h, 24 h	–		Sakuma *et al.* (2006)
DNA single- and double-strand breaks	HSF	1800 MHz, CW, PW(i); GSM	2 W/kg	1, 4, 24 h	–	Replication study. Previous results not confirmed.	Speit *et al.* (2007)
DNA single- and double-strand breaks	HTR	1817 MHz, PW; GSM	2 W/kg	1 h	–		Valbonesi *et al.* (2008)

Table 4.5 (continued)

End-point	Cells	Frequency	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	HTR	1800 MHz, CW, PW(i); GSM	2 W/kg	4–24 h	– with CW – with PW at 4 h + with PW at 16 h and 24 h	Differential response between CW and PW and exposure duration	Franzellitti *et al.* (2010)
DNA single- and double-strand breaks	LEP	1800 MHz, PW; GSM	1, 2, 3 W/kg	2 h	– at 1 and 2 W/kg + at 3 W/kg		Lixia *et al.* (2006)
DNA single- and double-strand breaks	LEP	1800 MHz, PW(i); GSM	1, 2, 3, 4 W/kg	2 h	– at 1 and 2 W/kg + at 3 and 4 W/kg		Yao *et al.* (2008)
DNA single- and double-strand breaks	LUF	2000 MHz, PW, CW; IMT	0.08 W/kg	2, 24 h	–		Sakuma *et al.* (2006)
DNA single- and double-strand breaks	LYB	813, 836 MHz, PW; iDEN, TDMA	2.4–26 mW/kg	2–21 h	±	Inconsistent results	Phillips *et al.* (1998)
DNA single- and double-strand breaks	LYB	813, 836, 835, 847 MHz, CW, PW; iDEN, TDMA, FDMA, CDMA	0.0024–0.026 W/kg, 3.2 W/kg	2–21 h	–		Hook *et al.* (2004a)
DNA single- and double-strand breaks	LYB	1800 MHz, PW; GSM	2 W/kg	6–24 h	–		Zhijian *et al.* (2010)
DNA single- and double-strand breaks	NUB	872 MHz, CW, PW; GSM	5 W/kg	1 h	–	Temperature-controlled conditions	Luukkonen *et al.* (2009)
DNA single- and double-strand breaks	NUB	872 MHz, CW, PW; GSM	5 W/kg	3 h	–	Temperature-controlled conditions	Luukkonen *et al.* (2010)
DNA single- and double-strand breaks	SHF	1800 MHz, PW (c, i)	2 W/kg	4–24 h	+	Controversial data	Diem *et al.* (2005)
DNA single- and double-strand breaks	SHF	1950 MHz, PW(c-i); UMTS	0.05–2 W/kg	4–48 h	+	Controversial data	Schwarz *et al.* (2008)

Table 4.5 (continued)

End-point	Cells	Frequency	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	SHF	900 MHz, PW; GSM	1 W/kg	24 h	–		Sannino *et al.* (2009b)
Foci	HFB, MST	905, 915, 1947 MHz, PW; GSM, UMTS	0.037, 0.039 W/kg	1–3 h	+ at 915MHz – at 905 MHz + at 1947 MHz	Decrease in 53BP1-foci, measured by immuno-staining	Markovà *et al.* (2010)
Spindle disturbance	HHH	835 MHz, PW; GSM	5–90 V/m	30 min	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Schmid & Schrader (2007)
Spindle disturbance	HHH	835 MHz, PW	62.5 mW/kg	10 min to 2 h	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Schrader *et al.* (2008)
Spindle disturbance	HHH	1060 MHz, CW	0.043–4.3 mW/cm^2	30 min	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Hintzsche *et al.* (2011)
Spindle disturbance	HHH	900 MHz, CW, PW	0.0115 W/kg	30 min	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Schrader *et al.* (2011)
8-OHdG, oxidative damage in DNA	SPR	1800 MHz	0.4–27.5 W/kg	16 h	+	Temperature controlled at 21 °C; maximum increase 0.4 °C during exposure.	De Iuliis *et al.* (2009)

+, increase; ±, equivocal; – , no effect; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; BUC, human buccal cells; (c, i), continuous and intermittent exposure; d, day; FDMA, frequency-division multiple access; FMCW, frequency-modulated continuous wave; GLB, glioblastoma cells; h, hour; HAC, human amniotic cells; HFB, human foreskin fibroblasts; HHH, hamster–human hybrid cells; HTR, trophoblast cells; iDEN, Integrated Digital Enhanced Network; IMT, International Mobile Telecommunication; LEP, lens epithelial cells; LUF, human fibroblasts from fetal lung; LYB, lymphoblastoid cells; min, minute; MST, mesenchymal stem cells; NUB, neuroblastoma cells; NR, not reported; SHF, skin human fibroblasts; SPR, sperm cells; TDAM, time-division multiple access; yr, year

neuroblastoma cells exposed to continuous- or pulsed-wave RF radiation at 872 MHz, with a SAR of 5 W/kg. In the studies mentioned above the alkaline comet assay was used to measure strand breakage in DNA.

(iii) Lens epithelial cells

Immortalized SRA01/04 human lens epithelial cells were exposed to pulsed-wave RF radiation at 1800 MHz (SAR, 1, 2 or 3 W/kg) for 2 hours to investigate induction of DNA breakage, which was measured by means of the alkaline comet assay. DNA-damage repair was evaluated by further incubation of the exposed cells for 30, 60, 120 or 240 minutes. There was a significant increase ($P < 0.05$) in DNA strand-breaks at a SAR of 3 W/kg immediately after exposure, which had decreased at 30 minutes, and had diminished to control levels at later time-points. At SARs of 1 and 2 W/kg, there were no significant differences between exposed cells and sham-exposed controls (Lixia *et al.*, 2006).

In a similar study, DNA strand breaks were measured in SRA01/04 human lens epithelial cells exposed to intermittent (5 minutes on, 10 minutes off) pulsed-wave RF radiation at 1800 MHz (SAR, 1, 2, 3, or 4 W/kg) for 2 hours. There was no effect on DNA single-strand breaks – measured with the alkaline comet assay – at SARs of 1 or 2 W/kg, but a significant increase at SARs of 3 or 4 W/kg ($P < 0.001$). At these two higher SAR values, there was no difference in the induction of DNA double-strand breaks, measured with the γH2AX-focus formation assay (Yao *et al.*, 2008).

(iv) Lung fibroblasts

Sakuma *et al.* (2006) exposed human IMR-90 fetal lung fibroblasts to pulsed-wave RF radiation at 2000 MHz (SAR, 80 mW/kg) for 24 hours, and observed no effect on induction of DNA strand breaks.

(v) Lymphoblastoid cells

Phillips *et al.* (1998) studied DNA strand-break induction in human Molt-4 lymphoblastoid cells exposed for 2, 3 or 21 hours to RF radiation at 813 or 835 MHz as iDEN (Integrated Digital Enhanced Network) and TDMA (time-division multiple access) signals, with very low SARs of 2.4, 24, 2.6 and 26 mW/kg. There was a general decrease in the number of strand breaks at lower SARs at 2 and 21 hours (but not at 3 hours), and inconsistent results at higher SARs, depending on the type of RF signal, power intensity and duration of exposure. Hook *et al.* (2004a) examined DNA strand-break induction in Molt-4 cells exposed to the same and additional signals (813.56–847.74 MHz) at the same and higher SARs (2.4 mW/kg–3.4 W/kg) than in the study by Phillips *et al.* (1998). No effect on DNA strand-break induction was noted. Zhijian *et al.* (2010) did not find any effect on DNA strand-break induction when human HMy2.CIR lymphoblastoid B-cells were exposed to pulsed-wave RF radiation at 1800 MHz (SAR, 2 W/kg), for 6–24 hours.

(vi) Skin fibroblasts

Diem *et al.* (2005) exposed human ES-1 skin fibroblasts to continuous or intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 1.2 or 2 W/kg) for 4–24 hours. The cells were examined visually and subjectively to evaluate DNA single- and double-strand breaks by use of the alkaline and neutral comet assays. A "tail factor" was devised to express the results. The authors concluded that: there was a significant increase in tail factor after a 16-hour exposure, with no further increase after 24 hours; and that intermittent exposure produced a stronger effect than continuous exposure.

In a study from the same group, Schwarz *et al.* (2008) used ES-1 cells exposed for 4–48 hours to continuous and intermittent RF radiation at 1950 MHz (UMTS), with a range of SAR values (0.05–2 W/kg). The results from the analyses of

DNA strand breaks by means of the comet assay indicated a significant increase in tail factor ($P < 0.02$) at SAR 0.05 W/kg. In addition, there was a significant increase ($P < 0.02$, at SAR 0.05 W/kg) in the frequency of micronuclei, which turned out be centromere-negative (suggesting a clastogenic effect). In a similar experiment in peripheral blood lymphocytes, there was no effect on the comet tail factor or micronucleus formation (see above). Several discussions about the mode of data acquisition in these two studies subsequently appeared in scientific journals (Rüdiger *et al.*, 2006; Vijayalaxmi *et al.*, 2006; Tuffs, 2008; Vogel, 2008; Wolf, 2008; Balzano, 2008; Kuster, 2008; Drexler & Schaller, 2009; Rüdiger, 2009b, c; Lerchl & Wilhelm, 2010; Baan, 2009).

Speit *et al.* (2007) performed independent experiments to replicate and confirm the results of the two studies mentioned above, by use of the same ES-1 skin fibroblasts, the same exposure system supplied by the same company, and the same laboratory protocols. The comet tail factor as well as computerized image-analysis were used to quantify the DNA strand breaks. The experiments were also performed in Chinese hamster V79 cells. The results showed no effect on DNA breakage either by the alkaline comet assay or by the micronucleus test, in either fibroblasts or V79 cells.

Skin fibroblasts established from healthy individuals or from subjects with Turner syndrome were exposed to 900 MHz pulsed-wave RF radiation (SAR, 1 W/kg). It was suggested that cells from patients with Turner syndrome were sensitive to the effects of weakly genotoxic agents (Scarfi *et al.*, 1997a, b). No effects on DNA strand-break induction or micronucleus formation were observed in either cell line (Sannino *et al.*, 2009b).

Markovà *et al.* (2010) observed no effect on 53BP1 foci in skin fibroblasts exposed to RF radiation at 905 MHz (SAR, 37 mW/kg). In contrast, a decrease was seen when the same cells were exposed at 915 or 1947 MHz at similar SAR levels [the Working Group noted that this technique assesses repair foci of DNA double-strand breaks; it is different from the comet assay used for analysis of DNA strand breaks in the other studies with skin cells discussed above].

(vii) Mesenchymal stem cells

Markovà *et al.* (2010) observed a decrease in the number of 53BP1 foci in mesenchymal stem cells exposed to RF radiation at 915 or 1947 MHz (GSM; SAR 37 and 39 mW/kg, respectively) for 1, 2, or 3 hours; no effect was noted after exposure at 905 MHz (SAR, 37 mW/kg).

(viii) Sperm cells

De Iuliis *et al.* (2009) studied purified human spermatozoa exposed to RF radiation at 1800 MHz (SAR, 0.4–27.5 W/kg) for 16 hours at 21 °C. With increasing SAR values, motility and vitality of the sperm cells were significantly reduced, while mitochondrial production of reactive oxygen species was significantly increased ($P < 0.001$). There was also a significant increase ($P < 0.05$) in formation of 8-OHdG adducts (measured immunochemically) and DNA fragmentation (measured with the TUNEL – terminal deoxynucleotidyl transferase dUTP nick end labelling – assay) at SARs of 2.8 W/kg and higher. The temperature during these experiments was kept at 21 °C; the highest observed exposure-induced temperature increase was +0.4 °C, at a SAR of 27.5 W/kg.

(ix) Trophoblast cells

Valbonesi *et al.* (2008) observed no effects on DNA strand-break induction in human HTR-8/SVneo trophoblast cells exposed to pulse-modulated RF radiation at 1817 MHz (SAR, 2 W/kg) for 1 hour.

Franzellitti *et al.* (2010) observed no effects on DNA strand-break induction in HTR-8/SVneo trophoblast cells exposed to continuous-wave RF radiation at 1800 MHz (SAR, 2 W/kg) for 4, 16 or 24 hours. Exposure to this radiation as pulsed-wave amplitude-modulated signals (GSM-217 Hz

and GSM-Talk), caused a significant increase in DNA strand breakage after all three treatment periods when the results of the comet assay were expressed as "% DNA in tail." The number of DNA strand breaks decreased rapidly during the 2 hours after exposure.

(c) Humans: interaction of RF radiation with known genotoxic agents

Some details on the exposure conditions to RF radiation and a short conclusion for each publication are presented in Table 4.6. Unless otherwise mentioned, the results discussed below refer to those observed in human peripheral blood lymphocytes exposed to RF radiation before, during or after exposure to a genotoxic agent.

(i) Chemotherapeutic drugs

Gadhia *et al.* (2003) reported a synergistic increase in chromosomal aberrations (rings, dicentrics) and SCE in lymphocytes collected from mobile-phone users and treated with mitomycin C (MMC) *in vitro*, compared with cells from controls (non-phone users) treated with MMC. This effect was stronger in mobile-phone users who smoked and consumed alcohol.

Maes *et al.* (2006) found no effect of treatment with MMC on induction of DNA strand breaks, chromosomal aberrations or SCE in lymphocytes obtained from workers at a mobile-phone company. In a series of experiments *in vitro*, the same authors reported a highly reproducible synergistic effect (Maes *et al.*, 1996), a weak synergistic effect (Maes *et al.*, 1997), an inconsistent synergistic effect (Maes *et al.*, 2000), or no synergistic effect (Maes *et al.*, 2001) of exposure to RF radiation on MMC-induced SCE. [The Working Group noted that the authors made several suggestions regarding possible mechanistic explanations for their findings, which were not pursued in detail. The authors also mentioned the possibility of a thermal effect, and indicated the incomplete characterization of the exposure conditions in their studies.]

Zhang *et al.* (2002) investigated a possible synergistic effect in human lymphocytes exposed to RF radiation at 2450 MHz (5 mW/cm^2; 2 hours) followed by treatment with MMC (0.0125–0.1 µg/ml; 24 hours). While RF radiation had no effect by itself, it significantly increased the effect of the higher doses of MMC on DNA strand-break induction and micronucleus formation. Since the temperature increase during the 2-hour exposure was less than 0.5 °C, the synergy was not likely to be due to thermal effects.

Baohong *et al.* (2005) exposed human lymphocytes to pulsed-wave RF radiation at 1800 MHz (SAR, 3 W/kg) for 2 hours, before, together with, or after incubation for 3 hours with four different chemicals. After these treatments, the cells were washed and processed for measurement of DNA strand-break induction at once or after further incubation for 21 hours. Exposure to RF radiation alone had no effect. All combinations of MMC or 4-nitroquinoline-1-oxide (4NQO) with RF radiation showed a significant increase in DNA breakage, compared with the results after incubation with the chemical alone. No such effect was observed when exposure to RF radiation was combined with treatment with bleomycin or methylmethane sulfonate (MMS), suggesting that interaction between RF radiation and different chemical mutagens could vary.

Hansteen *et al.* (2009a) found no effect on MMC-induced chromosomal aberrations after exposure of human lymphocytes to pulsed-wave RF radiation at 16.5 GHz (power density, 10 W/m^2) or 18 GHz continuous-wave RF radiation (power density 1 W/m^2) for 53 hours, with MMC added after 30 hours. Similar results were reported by the same authors for exposures to continuous-wave or pulsed-wave RF radiation at 2.3 GHz (power density, 10 W/m^2) in combination with MMC (Hansteen *et al.*, 2009b).

Sannino *et al.* (2009a) reported that pre-exposure of human lymphocytes to pulsed-wave RF

Table 4.6 Interaction between radiofrequency radiation and known genotoxic agents in human cells *in vitro*

End-point	Cells	Genotoxic agent	Frequency (MHz)	SAR or power density	Duration	Results	Comments	Reference
Chromosomal aberration	PBL	MMC or X-rays	900 MHz, PW; GSM	0.4–10 W/kg	RF radiation for 2 h, followed by X-rays for 1 min (1 Gy) or MMC for 72 h	–	No effect of RF radiation; no synergistic effects of RF radiation and MMC or X-rays	Maes *et al.* (2001)
Chromosomal aberration	PBL from phone users	MMC	890–960 MHz, PW; GSM	NR	Phone use for 1–3 h/d for 2 yr, MMC for 48 h	+	Increased gaps/dicentrics after RF radiation; synergistic effect of RF radiation with MMC	Gadhia *et al.* (2003)
Chromosomal aberration	PBL	Gamma-rays	2500 MHz 10 500 MHz, PW	627 W/kg 0.25 W/kg	40 s 5 min	–	MW oven used as 2.5 GHz source. No effect of RF radiation; no synergistic effect with gamma-rays	Figueiredo *et al.* (2004)
Chromosomal aberration	PBL	MMC	400–900 MHz, PW	NR	2.3 yr (> 1h/d) MMC for 72 h	–	Lymphocytes from exposed workers. No synergistic effect with MMC	Maes *et al.* (2006)
Chromosomal aberration	PBL	X-rays	935 MHz, PW; GSM	1 or 2 W/kg	1 min (1 Gy) X-rays, 24 h RF radiation	–	No effect of RF radiation; no synergistic effect with X-rays	Stronati *et al.* (2006)
Chromosomal aberration	PBL	X-rays	1950 MHz, PW, UMTS	0.5, 2 W/kg	X-rays 5 min, RF radiation for 24 h	+ at 2 W/kg – at 0.5 W/kg	No effect of RF radiation; synergistic effect of RF radiation with X-rays (4 Gy) at the higher SAR	Manti *et al.* (2008)
Chromosomal aberration	PBL	MMC	1800, 1650 MHz, CW, PW	0.1, 1 mW/cm^2	53 h; MMC added at 30 h	–	No effect of RF radiation; no synergistic effect with MMC	Hansteen *et al.* (2009a)
Chromosomal aberration	PBL	MMC	2300 MHz, CW, PW	1 mW/cm^2	53 h; MMC added at 30 h	–	No effect of RF radiation; no synergistic effect with MMC	Hansteen *et al.* (2009b)
Micronucleus formation	PBL	MMC	2450 MHz, PW	5 mW/cm^2	2 h, then MMC for 24 h	+	No effect of RF radiation; synergistic effect with MMC	Zhang *et al.* (2002)
Micronucleus formation	PBL	X-rays	935 MHz, PW; GSM	1 or 2 W/kg	1 min (1 Gy) X-rays, 24 h RF	–	No effect of RF radiation; no synergistic effect with X-rays	Stronati *et al.* (2006)
Micronucleus formation	PBL	MMC	900 MHz, PW; GSM	1.25 W/kg	20 h; MMC for 24 h	+	Reduction of MMC-induced MN frequency (adaptive response?) in lymphocytes from 4 out of 5 donors	Sannino *et al.* (2009a)

Table 4.6 (continued)

End-point	Cells	Genotoxic agent	Frequency (MHz)	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	PBL	MMC	2450 MHz, PW	5 mW/cm^2	2 h, then MMC for 24 h	+	No effect of RF radiation; synergistic effect with MMC	Zhang *et al.* (2002)
DNA single- and double-strand breaks	PBL	MMC, 4NQO	1800 MHz, PW; GSM	3 W/kg	2 h RF irradiation, 3 h with the chemical	+	No effect of RF radiation. Exposure to chemicals before, during or after RF irradiation showed a synergistic effect with MMC and 4NQO	Baohong *et al.* (2005)
DNA single- and double-strand breaks	PBL	BLM, MMS	1800 MHz, PW, GSM	3 W/kg	2 h RF radiation 3 h with the chemical	–	No effect of RF radiation. Exposure to chemicals before, during or after RF irradiation showed no synergistic effect with BLM and MMS	Baohong *et al.* (2005)
DNA single- and double-strand breaks	PBL	MMC	400–900 MHz, PW	NR	2.3 yr (> 1 h/d) MMC for 72 h	–	Lymphocytes from exposed workers. No synergistic effect with MMC	Maes *et al.* (2006)
DNA single- and double-strand breaks	PBL	X-rays	935 MHz, PW; GSM	1 or 2 W/kg	1 min (1 Gy) X-rays, 24 h RF	–	No effect of RF radiation; no synergistic effect with X-rays	Stronati *et al.* (2006)
DNA single- and double-strand breaks	PBL	UV	1800 MHz, PW; GSM	3 W/kg	1.5 or 4 h; just after UVC at 0.25–2.0 J/m^2	+ at 4 h + at 1.5 h	Effect with UV depended on exposure duration: decrease at 1.5 h, increase at 4 h	Baohong *et al.* (2007)
DNA single- and double-strand breaks	PBL	APC	835 MHz, PW; CDMA	1.2 W/kg	1 h RF irradiation and APC at 0.2 or 2 µg/ml	+	No effect of RF radiation; synergistic RF effect on aphidicolin-induced repairable DNA damage.	Tiwari *et al.* (2008)
DNA single- and double-strand breaks	NUB	Menadione	872 MHz, CW, PW; GSM	5 W/kg	1 h RF and 50 µM menadione	+ with CW – with PW	Differential effect of CW and PW with menadione	Luukkonen *et al.* (2009)
DNA single- and double-strand breaks	HSF	MX	900 MHz, PW; GSM	1 W/kg	24 h RF, 1 h MX at 25 µM	–	No synergistic effect on MX-induced SB	Sannino *et al.* (2009b)
DNA single- and double-strand breaks	PBL	X-rays	1800 MHz, PW(i); GSM	2 W/kg	24 h (on/off for 5/10 min) then 0.25–2 Gy of X-rays	–	No effect of RF radiation; no synergistic effect with X-rays on SB induction or repair	Zhijian *et al.* (2009)

Table 4.6 (continued)

End-point	Cells	Genotoxic agent	Frequency (MHz)	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	NUB	$FeCl_2$ + DEM	872 MHz, CW, PW; GSM	5 W/kg	1 h or 3 h RF; 1 h $FeCl_2$ ± DEM	–	No effect of RF radiation; no synergistic effect with free radical-inducing chemicals	Luukkonen *et al.* (2010)
DNA single- and double-strand breaks	LYB	DOX	1800 MHz, PW; GSM	2 W/kg	6–24 h RF; 2 h DOX	–	No effect of RF radiation; no synergistic effect with doxorubicin on induction of single- or double-strand breaks; effect on repair (?)	Zhijian *et al.* (2010)
Sister-chromatid exchange	PBL	MMC	954 MHz, PW; GSM	1.5 W/kg	2 h RF radiation 72 h MMC	+	No effect of RF radiation; highly reproducible synergistic effect with MMC	Maes *et al.* (1996)
Sister-chromatid exchange	PBL	MMC	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h RF radiation 72 h MMC	+	No effect of RF radiation: weak synergistic effect with MMC	Maes *et al.* (1997)
Sister-chromatid exchange	PBL	MMC	455.7 MHz, PW; car phone	6.5 W/kg	2 h (72 h MMC)	±	No effect of RF radiation; inconsistent synergistic effect with MMC	Maes *et al.* (2000)
Sister-chromatid exchange	PBL	MMC, X-rays	900 MHz, PW; GSM	0.4–10 W/kg	2 h (72 h MMC)	–	No effect of RF radiation; no synergistic effect with MMC or with X-rays	Maes *et al.* (2001)
Sister-chromatid exchange	PBL from phone users	MMC	890–960 MHz, PW; GSM	NR	1–3 h/d for 2 yr 48 h MMC	+	Increased SCE after RF radiation; synergistic effect with MMC	Gadhia *et al.* (2003)
Sister-chromatid exchange	PBL	MMC	400–900 MHz, PW	NR	72 h	–	No effect of RF radiation; no synergistic effect with with MMC	Maes *et al.* (2006)
Sister-chromatid exchange	PBL	X-rays	935 MHz, PW; GSM	1, 2 W/kg	24 h	–	No effect of RF radiation; no synergistic effect with X-rays	Stronati *et al.* (2006)

+, increase; ±, equivocal; – , no effect; 4NQO, 4-nitroquinoline-1-oxide; APC, aphidicolin; BLM, bleomycin; CW, continuous wave; d, day; DEM, diethyl maleate; $FeCl_2$, ferrous chloride; h, hour; HSF, human skin fibroblasts; (i), intermittent exposure; LYB, lymphoblastoid cells; min, minute; MMC, mitomycin C; MMS, methylmethane sulfonate; MX, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone; NUB, neuroblastoma cells; NR, not reported; PBL, peripheral blood lymphocytes; PW, pulsed wave

radiation at 900 MHz (peak SAR, 10 W/kg) for 20 hours reduced the incidence of MMC-induced micronucleus formation, suggesting that non-ionizing radiation is capable of inducing an "adaptive response" similar to that observed in several studies of ionizing radiation.

Zhijian *et al.* (2010) treated cultured human lymphoblastoid cells with doxorubicin (DOX) for 2 hours before, during and after exposure to pulsed-wave RF radiation at 1800 MHz (SAR, 2 W/kg). No significant effects on DOX-induced DNA strand-break formation were found.

(ii) Genotoxic chemicals

Tiwari *et al.* (2008) exposed human peripheral blood lymphocytes to RF radiation at 835 MHz (SAR, 1.17 W/kg) for 1 hour, with and without treatment with aphidicolin (APC; 0.2 or 2 μg/ml), an inhibitor of DNA repair. There was no effect on DNA strand-break induction of RF radiation by itself, or of the low dose of APC alone. There was a significant increase in DNA breakage after combined exposure of the cells to RF radiation with the low ($P = 0.025$) and the high dose ($P = 0.002$) of APC. Sannino *et al.* (2009b) found no effect on the number of DNA strand breaks induced by 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX) in skin fibroblasts from healthy individuals or from subjects with Turner syndrome exposed to pulsed-wave RF radiation at 900 MHz (SAR, 1 W/kg) for 24 hours, followed by treatment with MX for 1 hour.

Luukkonen *et al.* (2009) found a significant increase ($P < 0.01$) in the number of menadione-induced DNA strand breaks in cultured human SH-SY5Y neuroblastoma cells exposed to continuous-wave RF radiation at 872 MHz (SAR, 5 W/kg) and menadione (25 μM) for 1 hour, but not in cells exposed to pulsed-wave RF radiation (GSM) and menadione. In a subsequent study with the same cell type, the same authors did not observe an increase in the number of DNA strand breaks after exposure to continuous- or pulsed-wave RF radiation at the same frequency and SAR (872 MHz; 5 W/kg), with or without ferrous chloride and diethyl maleate (the latter compound was added to enhance the free-radical production induced by the former) (Luukkonen *et al.*, 2010).

(iii) Ionizing radiation

Figueiredo *et al.* (2004) reported no effects of RF radiation on the induction of chromosomal aberration by gamma radiation in human lymphocytes exposed to pulsed-wave RF radiation at 2.5 or 10.5 GHz (SAR, 627 and 0.25 W/kg, respectively) for 40 seconds or 5 minutes, respectively, followed 2 hours later by exposure to 1.5 Gy gamma radiation from a cobalt-60 source. No effect was observed after exposure to RF radiation alone. Stronati *et al.* (2006) found no effect of RF radiation on X-ray-induced DNA strand breaks, chromosomal aberrations, micronucleus formation or SCE in human peripheral blood lymphocytes exposed to pulsed-wave RF radiation at 935 MHz (SAR 1 or 2 W/kg) for 24 hours, combined with 1.0 Gy of 250 kVp X-rays, given for 1 minute immediately before or after exposure to RF radiation. In the FISH assay used by Manti *et al.* (2008), there was no effect of RF radiation on X-ray-induced chromosomal aberrations in human lymphocytes exposed to 4 Gy of X-rays immediately before exposure to pulsed-wave RF radiation at 1950 MHz (SAR, 0.5 W/kg), while a small but statistically significant increase ($P = 0.036$) was observed at a SAR of 2 W/kg. Zhijian *et al.* (2009) did not find an effect of RF radiation on DNA strand breaks induced by X-rays, or their repair, in lymphocytes exposed to intermittent (5 minutes on, 10 minutes off) pulsed-wave RF radiation at 1800 MHz (SAR, 2 W/kg) for 24 hours, followed by exposure to X-rays (0.25–2.0 Gy).

(iv) Ultraviolet radiation

Baohong *et al.* (2007) exposed peripheral blood lymphocytes to 254 nm ultraviolet radiation (UVC) at 0.25–2.0 J/m^2, followed by RF

radiation at 1800 MHz (SAR, 3 W/kg), for 1.5 or 4 hours. The number of UV-induced DNA strand breaks decreased after exposure to RF radiation for 1.5 hours, and increased after exposure for 4 hours.

(d) Mammalian cells (non-human)

See Table 4.7

(i) 800–1800 MHz

Mouse C3H 10T½ fibroblast cells (both exponentially growing and in plateau phase) were exposed to RF radiation at 835.62 MHz as a frequency-modulated continuous-wave (FMCW) signal, or to RF radiation as a code-division multiple access (CDMA) signal at 847.74 MHz (SAR, 0.6 W/kg), for up to 24 hours. The alkaline comet assay was used to measure induction of DNA strand breaks. No significant differences were observed between the results obtained with FMCW or CDMA radiation and the sham-exposed negative controls (Malyapa *et al.*, 1997b). The same authors did not find any effects in a similar experiment with continuous-wave RF radiation at 2450 MHz (SAR, 0.7 or 1.9 W/kg) (Malyapa *et al.*, 1997a).

C3H 10T½ fibroblast cultures (exponentially growing or in the plateau phase) were exposed to RF radiation at 847.74 MHz as a CDMA signal, or to RF radiation at 835.62 MHz as a FDMA signal (SAR, 3.2–5.1 W/kg) for 2, 4, or 24 hours. The alkaline comet assay was used to measure induction of DNA strand breaks. No statistically significant change was found in tail moment or tail length for cells that had been exposed to RF radiation (CDMA or FDMA), compared with sham-exposed controls. Furthermore, in cells exposed for 2 hours to RF radiation, a post-incubation of 4 hours did not result in significant changes in tail moment or tail length (Li *et al.*, 2001).

Exponentially growing or plateau-phase C3H 10T½ cells – derived from mouse-embryo fibroblasts – were exposed to RF radiation at 835.62 MHz, as CDMA (SAR, 3.2 or 4.8 W/kg) signal, or at 847.74 MHz as frequency-division multiple access (FDMA) signal (SAR, 3.2 or 5.1 W/kg), for 3, 8, 16 or 24 hours. No significant exposure-related differences in micronucleus formation were found for either plateau-phase cells or exponentially growing cells (Bisht *et al.*, 2002).

Diem *et al.* (2005) reported the results of an alkaline comet assay with SV40-transformed rat granulosa cells exposed to continuous or intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 1.2 or 2 W/kg) for 4–24 hours. Both continuous and intermittent exposures induced DNA single- and double-strand breaks, with the greatest effect found with intermittent exposure. Speit *et al.* (2007) independently repeated some of the experiments with V79 Chinese hamster cells, using the same equipment and exposure conditions (1800 MHz; 2 W/kg SAR; continuous wave with intermittent exposure). No effects of exposure to RF radiation were found in assays for DNA strand-break induction and micronucleus formation.

Chinese hamster lung cells exposed to intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 3 W/kg) for 24 hours contained an increased number of γ-H2AX foci – a measure of DNA double-strand breaks – compared with sham-exposed cells. There was no effect after a 1-hour exposure to RF radiation (Zhang *et al.*, 2006).

Because auditory cells could be exposed to RF radiation at frequencies at which mobile phones operate, Huang *et al.* (2008) used HEI-OC1 immortalized mouse auditory hair cells to characterize their response to exposure to RF radiation at 1763 MHz (SAR, 20 W/kg), in a CDMA exposure chamber for 24 or 48 hours. No changes were found in the phase-distribution of the cell cycle, DNA strand-break induction, stress response, or gene-expression profiles in the exposed cells, compared with sham-exposed controls.

Table 4.7 Genetic and related effects of exposure to radiofrequency radiation in experimental systems *in vitro*

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
pBluescript SK(+) plasmid, DNA strand breaks (DNA degradation *in vitro*)	835 MHz, CW; SAR, 4 W/kg; 48 h	-	Exposure to RF radiation did not change the rate of degradation of plasmid pBluescript SK(+) exposed to H_2O_2 (Fenton-type reaction) as an indicator.	Chang *et al.* (2005)
Escherichia coli WP2 *uvrA*, reverse mutation	835 MHz, CW; SAR, 4 W/kg; 48 h	4-NQO, for 48 h during exposure to RF radiation	RF radiation increased 4-NQO-induced mutation rate in *Escherichia coli* WP2.	Chang *et al.* (2005)
Escherichia coli WP2 *uvrA*, reverse mutation	2450 MHz; SAR, 5–200 W/kg; 30 min	-	No effect on mutagenicity	Koyama *et al.* (2007)
Salmonella typhimurium TA98, TA100, TA102 and TA1535, reverse mutation	835 MHz, CW; SAR, 4 W/kg; 48 h	4-NQO, cumene hydroperoxide (CHP) sodium azide (SA) for 48 h during exposure to RF radiation	RF radiation increased CHP-induced mutation rate in TA102, had no effect on SA-induced revertants in TA100, and reduced SA-induced mutation rate in TA1535	Chang *et al.* (2005)
Salmonella typhimurium TA98, TA100, TA1535 and TA1537; reverse mutation	2450 MHz; SAR, 5–200 W/kg; 30 min	-	No effect on mutagenicity	Koyama *et al.* (2007)
Saccharomyces cerevisiae, gene-specific forward mutation at *CAN1*	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on mutation rates at *CAN1* ± MMS	Gos *et al.* (2000)
Saccharomyces cerevisiae, induction of respiration-deficient (*petite*) clones (loss of mitochondrial function)	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on the frequency of *petite* colony formation ±MMS	Gos *et al.* (2000)
Saccharomyces cerevisiae, intrachromosomal deletion-formation assay	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on formation of intrachromosomal deletions ±MMS	Gos *et al.* (2000)
Saccharomyces cerevisiae, intra-genic recombination assay in the *ADE2* gene	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on rates of intragenic recombination ± MMS	Gos *et al.* (2000)
Xenopus laevis; DNA SSB measured in erythrocytes sampled immediately after exposure	8800 MHz pulsed-wave; peak power, 65 kW; SAR, 1.6 W/kg; 40 min	-	No indication of non-thermal effects. Observed DNA damage probably due to temperature rise	Chemeris *et al.* (2004)
C3H10T½ mouse; DNA SSB measured in fibroblasts, sampled immediately and up to 4 h after exposure	2450 MHz CW; SAR, 0.7 and 1.9 W/kg; 2, 4 and 24 h	-	No effect	Malyapa *et al.* (1997a)

Table 4.7 (continued)

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
C3H10T½ mouse; DNA SSB measured in fibroblasts, sampled immediately exposure	835.62 MHz FMCW and 847.7 MHz, CDMA CW; SAR, 0.6 W/kg; 2, 4, 24 h	-	No effect	Malyapa *et al.* (1997b)
C3H10T½ mouse; DNA SSB measured in fibroblasts, sampled immediately and 4 h after exposure	835.6 MHz FDMA and 847.7 MHz FDMA; SAR, 3.2 and 5.1 W/kg; 2, 4 and 24 h exposure	-	No effect	Li *et al.* (2001)
C3H10T½ mouse; DNA SB, DNA–DNA and DNA–protein cross-links measured in fibroblasts	2450 MHz CW; SAR, 1.9 W/kg; 2 h exposure followed by 4 Gy gamma-rays	Gamma radiation	No effect of RF radiation on SB. No reduction by RF radiation of DNA migration induced by gamma-rays. No induction of DNA–protein crosslinks or changes in amount of DNA-associated protein by RF radiation	Lagroye *et al.* (2004b)
HEI-OC1 (immortalized mouse auditory hair) cells; DNA damage, stress response and gene expression	1763 MHz; SAR, 20 W/kg; CDMA; continuous exposure for 24 or 48 h		No effect on cellular responses, including cell-cycle distribution, DNA damage, stress response or gene expression	Huang *et al.* (2008)
L5178Y *Tk*$^{+/-}$ mouse lymphoma cells (DNA damage) and Chinese hamster lung fibroblasts (chromosomal aberrations, CA)	835 MHz; SAR, 4 W/kg; exposure for 48 h, alone or combined with chemicals	CPA, 4-NQO	No effect on DNA damage or CA. No effect on EMS-induced CA. Significant increase in CPA- and 4NQO-induced DNA damage.	Kim *et al.* (2008a)
Chinese hamster V79 cells; DNA damage (SSB, DSB)	1800 MHz; CW or pulsed-wave; continuous or intermittent (5 min on, 10 min off); SAR, 2 W/kg; exposure 1–24 h	-	No induction of DNA damage found in independent repeat experiments.	Speit *et al.* (2007)
Rat granulosa cells; DNA damage (SSB, DSB), sampled immediately after exposure	1800 MHz; CW or pulsed-wave; continuous and intermittent (5 min on, 10 min off); SAR, 2 W/kg; exposure 1–24 h	-	Induction of DNA SSB and DSB after 16 h intermittent exposure, at different mobile-phone modulations. Objections were raised to the analysis of the data	Diem *et al.* (2005)
Chinese hamster V79 cells; DNA synthesis, incorporation of [^{3}H] thymidine	7700 MHz; 300 mW/cm^2; 15, 30, 60 min	-	Cells are blocked in entering S-phase	Garaj-Vrhovac *et al.* (1990b)

Table 4.7 (continued)

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
Chinese hamster lung cells; DNA damage, gamma-H2AX focus formation	1800 MHz; intermittent (5 min on, 10 min off); SAR, 3.0 W/kg; for 1 or 24 h	-	RF radiation (24 h exposure, not 1 h) caused gamma-H2AX focus formation. A cell was classified positive when it contained more than five foci.	Zhang *et al.* (2006)
L5178Y $Tk^{+/-}$ mouse lymphoma cells; gene mutation	2450 MHz, pulsed-wave; power density, 488 W/m^2; SAR, 30 or 40 W/kg; 4 h, together with MMC (at lower SAR) of proflavin (at higher SAR).	-	No effect of RF radiation alone. No influence by RF radiation on cell-growth inhibition or on MMC- or proflavin-induced mutagenesis	Meltz et al. (1989, 1990)
Chinese hamster ovary CHO K1 cells; gene mutation *Hprt* locus	2450 MHz, SAR, 5–200 W/kg; 2 h	Bleomycin, for 1 h before irradiation	RF radiation (200 W/kg) increased *Hprt* mutation frequency by itself, and increased bleomycin-induced *Hprt* mutations (100 and 200 W/kg). Effects may be due to hyperthermia	Koyama *et al.* (2007)
Chinese hamster ovary cells; SCE	2450 MHz, pulsed-wave; 490 W/m^2; SAR, 33.8 W/kg; 2 h	Simultaneous exposure to adriamycin	No effect of RF radiation alone. No effect on adriamycin-induced SCE	Ciaravino *et al.* (1991)
C3H10T½ mouse fibroblasts; micronucleus formation	835.6 MHz CW, FDMA and 847.7 MHz CW, CDMA; SAR, 3.2 and 5.1 W/kg	-	No increase in frequency of micronucleus formation	Bisht *et al.* (2002)
Chinese hamster V79 cells; micronucleus formation	7700 MHz; 30 mW/cm^2 ; 15, 30, 60 min	-	Increased micronucleus formation	Garaj-Vrhovac *et al.* (1991)
Chinese hamster ovary CHO-K1 cells; micronucleus formation	2450 MHz; SAR, 13, 39, 50, 78, 100 W/kg; 18 h	Bleomycin	Increased micronucleus frequency after RF radiation, and potentiation by RF radiation of bleomycin-induced micronucleus formation, both at SARs ≥ 78 W/kg	Koyama *et al.* (2003)
Chinese hamster ovary CHO-K1 cells; micronucleus formation	2450 MHz; SAR, 5, 10, 20, 50, 100, 200 W/kg; 2 h	Bleomycin	Increased micronucleus formation at SARs of 100 and 200 W/kg. No combined effect of RF and bleomycin	Koyama *et al.* (2004)
Chinese hamster V79 cells; micronucleus formation	1800 MHz; CW or pulse-wave; continuous and intermittent (5 min on, 10 min off), 1–24 h; SAR, 2 W/kg	-	No effect found. This study was aimed at replicating earlier findings.	Speit *et al.* (2007)
Bovine lymphocytes; micronucleus formation	9000 MHz, 70 W/kg CW; 10 min	MMC	Increased micronucleus frequency after RF radiation; significant increase by RF radiation of MMC-induced micronuclei.	Scarfi *et al.* (1996)

Table 4.7 (continued)

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
Mouse m5S cells; chromosomal aberrations	2450 MHz CW or PW; SAR, 5, 10, 20, 50, 100 W/kg; 2 h	-	No effect	Komatsubara *et al.* (2005)
Chinese hamster V79 cells; chromosomal aberrations	7700 MHz, 300 mW/cm^2; 15, 30, 60 min	-	Induction of chromosomal aberrations	Garaj-Vrhovac *et al.* (1990b)
Chinese hamster ovary cells; chromosomal aberrations	2450 MHz pulsed-wave; 490 mW/cm^2, SAR, 33.8 W/kg, 2 h	Simultaneous exposure to adriamycin or MMC	No effect of RF radiation alone No effect by RF radiation on aberrations induced by adriamycin or MMC	Kerbacher *et al.* (1990)
Chinese hamster V79 cells; chromosomal aberrations (structural)	7700 MHz, 30 mW/cm^2, 15, 30, 60 min	-	Increased frequency of chromosomal aberrations, including dicentrics and ring chromosomes	Garaj-Vrhovac *et al.* (1991)
Chinese hamster ovary cells; cell-cycle progression	2450 MHz pulsed-wave; 490 mW/cm^2, SAR, 33.8 W/kg, 2 h	Simultaneous exposure to adriamycin	No effect of RF radiation alone No influence on cell-cycle progression caused by adriamycin	Ciaravino *et al.* (1991)
Chinese hamster V79 cells; cell growth (cell count, microtubule structure)	935 MHz; SAR: 0.12 W/kg; 1, 2, 3 h	-	Alteration of microtubule stucture after a 3-h exposure; significantly decreased growth was noted in cells exposed for 3 h, at 3 d after exposure	Pavicic & Trosic, (2008)
Chinese hamster V79 cells; cell-proliferation kinetics, analysis of microtubule structure, mitotic index	935 MHz CW; SAR, 0.12 W/kg; 1, 2, 3 h	-	Alteration of microtubule structure; no effect on mitotic index. Cell proliferation was reduced at 72 h after exposure in cells exposed for 3 h. Slower cell-division kinetics	Trosić & Pavicić (2009)
Chinese hamster V79 cells; survival	7700 MHz; 0.5, 10, 30 mW/cm^2; 10, 20, 30, 60 min	-	After 8 days of post-incubation: reduced cell survival related to power density and exposure time	Garaj-Vrhovac *et al.* (1991)

4-NQO, 4-nitroquinoline 1-oxide; CA, chromosomal abberations; CDMA, code-division multiple access; CHP, cumene hydroperoxide; CPA, cyclophosphamide; CW, continuous wave; DSB, DNA double-strand breaks; FDMA, frequency-division multiple access; h, hour; *Hprt*, hypoxanthine-guanine phosphoribosyl transferase gene; min, minute; MMC, mitomycin C; MMS, methylmethane sulfonate; MN, micronuclei; SA, sodium azide; SCE, sister-chromatid exchange; SSB, DNA single-strand breaks

The alkaline comet assay and a test for chromosome aberrations *in vitro* were used to investigate the effects of 835 MHz RF radiation (4 W/kg), alone and in combination with the clastogens cyclophosphamide (CP), 4NQO and ethylmethane sulfonate (EMS), in L5178Y $Tk^{+/-}$ mouse-lymphoma cells (to assess DNA breakage) and in Chinese hamster lung fibroblasts (to measure chromosome aberrations). In the latter cells, no effect was observed from RF radiation, alone or in combination with CP or EMS, but in the mouse-lymphoma cells a potentiating effect was noted on DNA strand-break induction after exposure to RF radiation following treatment with CP or 4NQO (Kim *et al.*, 2008a).

V79 Chinese hamster cells were exposed for 1, 2, or 3 hours to RF radiation at 935 MHz, generating an electric field-strength of 8.2 ± 0.3 V/cm and an average SAR of 0.12 W/kg. The microtubule structure in these cells was analysed by use of an immunocytochemical method. After 3 hours of exposure, microtubules in exposed cells were found to be altered compared with those in unexposed control cells. Three days after exposure, cell proliferation was significantly decreased in samples that had been exposed for 3 hours. Exposure to RF radiation at 935 MHz affects the structure of microtubule proteins, which consequently may obstruct cell growth (Pavicic & Trosic, 2008; Trosić & Pavicić, 2009).

(ii) 2450 MHz

The assay for forward mutation at the thymidine kinase locus in L5178Y mouse lymphoma cells was used to investigate the effects of a 4-hour exposure to RF radiation at 2450 MHz (power density, 48.8 mW/cm^2; SAR, 30 W/kg), alone and in the presence of the chemical mutagen MMC (0.1, 0.2, 0.3 µg/ml). Exposure to RF radiation alone was not mutagenic, and it did not alter the effects of MMC with regards to cell proliferation or mutation induction (Meltz *et al.*, 1989). A similar experiment involving exposure to RF radiation combined with proflavin – a DNA-intercalating drug – gave similar results (Meltz *et al.*, 1990).

In a cytogenetic study, CHO cells were exposed to pulsed-wave RF radiation at 2450 MHz (SAR, 33.8 W/kg), for 2 hours in the absence or presence of MMC (0.075 or 0.1 µg/ml) or adriamycin (0.175 µg/ml). The experimental conditions resulted in a maximum temperature increase of 3.2 °C. With respect to the induction of chromosomal aberrations, no effect was found that could be ascribed to the exposure to RF radiation (Kerbacher *et al.*, 1990).

CHO cells were exposed simultaneously to adriamycin (10^{-6} M) and pulsed-wave RF radiation at 2450 MHz (SAR, 33.8 W/kg) for 2 hours, or to adriamycin only. There was no effect of exposure to RF radiation on adriamycin-induced changes in cell progression or SCE frequency (Ciaravino *et al.*, 1991).

Micronucleus formation in Chinese hamster ovary (CHO) K1 cells was measured after exposure of the cells to RF radiation at 2450 MHz in four different scenarios: (1) exposure for 18 hours at average SARs of 13, 39 or 50 W/kg (input power, 7.8 W), which had no effect on micronucleus formation; (2) exposures corresponding to SARs of 78 or 100 W/kg (input power, 13 W), which produced a significant increase ($P < 0.01$) in micronucleus frequency; (3) treatment with the clastogenic compound bleomycin alone, or with bleomycin followed by irradiation for 18 hours at SARs of 25, 78 or 100 W/kg, which resulted in enhancement by RF radiation (at SAR values of 78 and 100 W/kg) of the effect of bleomycin alone; and (4) incubation at 39 °C for 18 hours as a high-temperature control; this last experiment also showed an increase in micronucleus frequency, albeit less strong than that after exposure to RF radiation. In a subsequent study, the authors reported a significant increase in micronucleus formation in cells exposed to RF radiation at 2450 MHz at SARs of 100 or 200 W/kg for 2 hours, but no effect of the combined exposure to RF radiation and bleomycin. Sham-exposures

at higher temperatures (38–42 °C) also increased the frequency of micronuclei, which indicates that the effects at the high SAR levels may have been thermal in nature (Koyama *et al.*, 2003, 2004).

C3H 10T½ mouse fibroblasts were exposed to continuous-wave RF radiation at 2450 MHz (SAR, 1.9 W/kg) for 2 hours and processed for measurement of alkali-labile DNA damage and/or DNA–protein or DNA–DNA crosslinks. No effect was noted for any of these end-points (Lagroye *et al.*, 2004b).

The induction of chromosomal aberrations was investigated in murine m5S cells exposed to continuous- or pulsed-wave RF radiation at 2450 MHz (average SARs of 5, 10, 20, 50 or 100 W/kg) for 2 hours. No significant differences were observed following exposure at any SAR compared with sham-exposed controls. There was also no difference between exposure to continuous-wave and pulsed-wave RF radiation (Komatsubara *et al.*, 2005).

CHO-K1 cells were exposed to RF radiation at 2450 MHz (SAR, 5–200 W/kg) for 2 hours, after which *Hprt* gene mutations were scored. There was no mutation induction by exposure to RF radiation alone. An increase in the mutation frequency was found in cells exposed to RF radiation (SAR, 100 or 200 W/kg) in combination with bleomycin, but this may have been a thermal effect (Koyama *et al.*, 2007).

(iii) 7000–9000 MHz

Cultured V79 Chinese hamster cells were exposed to continuous-wave RF radiation at 7700 MHz (power density, 30 mW/cm^2) for 15, 30, or 60 minutes. In comparison with the controls, there was a higher frequency of specific chromosome lesions and a reduction in the incorporation of [^{3}H]thymidine, showing inhibition of entry into S-phase (Garaj-Vrhovac *et al.*, 1990b).

In a further study, the same authors reported a decrease in the number of V79 cell colonies, which was related to the power density and the duration of exposure. Significantly higher frequencies of specific chromosomal aberrations – dicentrics, ring chromosomes – and micronuclei were observed in the exposed cells (Garaj-Vrhovac *et al.*, 1991).

Cultures of bovine *(Bos taurus* L.) peripheral blood lymphocytes were exposed to RF radiation at 9000 MHz (SAR, 70 W/kg) for 10 minutes. To evaluate possible cooperative effects with a chemical mutagen, some exposed cultures were also treated with MMC. Exposure to RF radiation induced a statistically significant increase in micronucleus formation, both in the presence ($P < 0.01$) and absence ($P < 0.001$) of MMC (Scarfi *et al.*, 1996).

(e) Non-mammalian cells

See Table 4.7

Mutagenic or recombinogenic effects of RF radiation at 900 MHz (GSM; SAR, 0.13 and 1.3 W/kg) were investigated in the yeast *Saccharomyces cerevisiae*. Mutation rates were monitored with a widely used gene-specific assay for forward mutation in the *CAN1* gene, which encodes arginine permease (gene-inactivating mutations lead to canavanine resistance) and with an assay measuring induction of respiration-deficient "*petite*" clones (small colonies) that have lost mitochondrial function. The recombinogenic effect of RF radiation was investigated with an assay for intrachromosomal deletion and an assay for intragenic recombination at the *ADE2* gene, which encodes an enzyme involved in purine (adenine) biosynthesis. Exposure of *S. cerevisiae* to RF radiation under these conditions did not result in recombinogenic or mutagenic effects (Gos *et al.*, 2000).

The effects of a 40-minute exposure to pulsed-wave RF radiation at 8800 MHz (SAR, 1.6 W/kg; pulse width, 180 ns; peak power, 65 kW; repetition rate, 50 Hz) were investigated in erythrocytes of the frog *Xenopus laevis* by means of the alkaline comet assay. The temperature rise in the blood samples at steady-state was 3.5 ± 0.1 °C.

The results showed that the increase in DNA damage after exposure was associated with the increase in temperature; in this experiment, no non-thermal effects on frog erythrocytes *in vitro* were noted (Chemeris *et al.*, 2004).

The effects of exposure to RF radiation at 835 MHz (SAR, 4 W/kg) for 48 hours were examined in assays for mutagenicity in bacteria. RF radiation was not directly mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, or in *Escherichia coli* strain WP2 *uvrA*. It significantly enhanced the mutagenicity of 4NQO in *E. coli* strain WP2 *uvrA* and of cumene hydroperoxide in *S. typhimurium* strain TA102. In a test for DNA degradation, no change in the rate of degradation (formation of DNA strand breaks) was observed with plasmid pBluescript SK(+) exposed to H_2O_2 (Fenton-type reaction) as an indicator (Chang *et al.*, 2005).

Mutagenicity tests were conducted in different bacterial strains (*S. typhimurium* TA98, TA100, TA1535 and TA1537, and *E. coli* WP2 *uvrA*) exposed to RF radiation at 2450 MHz (SAR, 5–200 W/kg) for 30 minutes. No effects were found in any of the strains tested (Koyama *et al.*, 2007).

[The Working Group noted that while several studies showed positive responses at high SAR values, some of these were due to thermal effects. The Working Group concluded that there was weak evidence that exposure to RF radiation is genotoxic in experimental systems in mammalian and non-mammalian cells *in vitro*.]

4.2 Effects of low-level exposure to RF radiation on the immune system

In this section, some studies that assess the effects of RF radiation on the immune system are discussed (see review by Jauchem, 2008).

4.2.1 *Immunotropic effects of exposure to RF radiation in humans*

[In general, occupational studies in this Section included small numbers of subjects and generally failed to control for possible confounders.]

Dmoch & Moszczyński (1998) measured immunoglobulin concentrations and proportions of different subsets of T lymphocytes in blood samples from 52 workers at television-retransmission and satellite-communication centres, exposed to RF radiation at 6–12 GHz. Concentrations of IgG and IgA immunoglobulins, and cell counts of total lymphocytes and T8 lymphocytes were increased, whereas the number of natural killer (NK) cells and the ratio of T-helper/T-suppressor cells were decreased, compared with the values in 30 non-exposed controls. There was no change in IgM concentrations. In an extension of this study, Moszczyński *et al.* (1999) performed a similar analysis with blood samples from radar operators. In this case, IgM concentrations were elevated and T8 lymphocyte cell-counts were decreased. The different results obtained in these two professional groups with respect to immunological parameters and blood-cell counts suggested that the effect of RF radiation on the immune system depends on the character of the exposure.

Tuschl *et al.* (1999) investigated the effects of long-term handling of various types of diathermy equipment – operating at frequencies of 27, 434, or 2450 MHz – on the immune system of medical personnel, by analysis of blood samples collected from physiotherapists operating these devices. Eighteen exposed subjects and 13 controls matched for sex and age were examined. Total leukocyte/lymphocyte counts and the proportion of leukocyte subpopulations were determined by use of flow cytometry and monoclonal antibodies to cell-surface antigens. In addition, lymphocyte activity was measured to quantify subpopulations of immunocompetent cells.

Lymphocytes were stimulated by the mitogen PHA and proliferation was measured by flow cytometry. No statistically significant differences between the exposed personnel and the controls were found. In both groups, all immune parameters were within normal ranges.

Radon *et al.* (2001) investigated the effects of RF radiation at 900 MHz (pulse frequency, 217 Hz; power density, 1 W/m^2) used in modern digital wireless telecommunication (GSM standard), in eight healthy male volunteers exposed in a specifically designed, shielded experimental chamber. The circularly polarized electromagnetic field applied was transmitted by an antenna positioned 10 cm behind the head of the volunteer, who was sitting upright. In double-blind trials, each volunteer underwent a total of 20 randomly allotted 4-hour periods of exposure and sham exposure, equally distributed during day and night. The salivary concentrations of IgA – as well as those of melatonin, cortisol and neopterin – did not differ significantly between the exposed and the sham-exposed subjects.

Yuan *et al.* (2004) investigated the effect of low-intensity, 170 MHz RF radiation on immune parameters in occupationally exposed workers. Blood-sample analysis showed no marked change in IgA concentrations, whereas those of IgM and IgG were significantly increased ($P < 0.01$) in the exposed group compared with those in non-exposed controls.

Kimata (2005) exposed 15 patients with atopic eczema dermatitis syndrome (AEDS) to RF radiation from a mobile phone (SAR, 1.62 W/kg) for 30 minutes. A second group of 15 patients was sham-exposed. In a repeat experiment 2 weeks later, the groups were switched with respect to exposure/sham-exposure. Before and after each study, mononuclear cells were stimulated with latex, the allergen to which the patients were sensitive. The production of latex-specific immunoglobulin E (IgE) was significantly increased ($P < 0.01$) after exposure to RF radiation.

[The Working Group noted that studies of humans exposed to RF radiation provided weak evidence for effects on the humoral immune system.]

4.2.2 *Immunotropic effects of exposure to RF radiation in experimental animals: studies* in vivo

See Table 4.8

(a) Mouse

Smiałowicz *et al.* (1983) exposed male CBA/J mice to 2450 MHz continuous-wave RF radiation (power density, 5, 15, 30 mW/cm^2; SAR, 3.5, 10.5, 21 W/kg, respectively) for 90 minutes per day for 2 or 9 days, and studied the effects on the activity of NK cells and the mitogen-induced response of lymphocytes. There was no consistent difference in the mitogen response of spleen cells from irradiated mice and sham-irradiated mice, while a significant suppression of NK activity was seen at the highest exposure intensity. NK activity returned to normal within 24 hours after exposure.

Veyret *et al.* (1991) exposed BALB/c mice to pulsed-wave RF radiation at 9400 MHz (1 µs pulses at 1000/second), both with and without amplitude modulation (AM) by a sinusoid signal at discrete frequencies between 14 and 41 MHz. Mice were immunized with sheep erythrocytes and exposed to RF radiation (30 µW/cm^2; whole-body SAR, 0.015 W/kg) for 10 hours per day, for 5 days. The antibody response to sheep erythrocytes was measured by the plaque-forming assay. In the absence of AM, there was not much change in immune responsiveness. Exposure to RF radiation with AM at 21 or 32 MHz led to significant enhancement of the response, while there was a decrease in the number of plaque-forming cells with AM at 14, 36, or 41 MHz.

Elekes *et al.* (1996) studied the effects of continuous-wave (CW) or amplitude-modulated (AM) RF radiation at 2450 MHz in male

Table 4.8 Immunotropic effects of exposure to radiofrequency radiation in experimental animals *in vivo*

Experimental system	Exposure conditions	Results	Reference
CBA/J mice	2450 MHz PW; SAR, 3.5, 10.5 and 21 W/kg; 1.5 h/d for 2, 3, 9 d	No increase in mitogenic response of splenic lymphocytes	Smiałowicz *et al.* (1983)
BALB/c mice	9400 MHz PW, AM; 30 μW/cm^2; whole-body SAR, ~0.015 W/kg; 10 h/d for 5 d	Significant increase in numbers of PFC at AM frequencies 21 and 32 MHz; significant decrease at 14, 36, 41 MHz.	Veyret *et al.* (1991)
BALB/c mice	2450 MHz CW or AM (50 Hz square wave); SAR, 0.14 W/kg; 3 h/d for 6 d	Increase in the number of antibody-producing cells in the spleen of małe mice; no effect in female mice.	Elekes *et al.* (1996)
C57BL/6 mice	900 MHz (GSM); SAR, 1 or 2 W/kg; 2 h/d for 1, 2, 4 wk	No substantial effect on T- and B-cell compartments. Transient increase of interferon-γ after 1 week of exposure, not at 2 or 4 wk	Gatta *et al.* (2003)
Mice [strain not given]	42 GHz; 105 μW/cm^2; 20 min/d for 1–14 d	Strong effect on indices of non-specific immunity. Phagocytic activity of neutrophils was suppressed by 45–50% within 2–3 h after a single exposure, remained suppressed for 1 d, and was restored to normal during 3 d. Blood leukocytes were increased after exposure for 5 d.	Kolomytseva *et al.* (2002)
NMR1 mice, exposed in the far-field zone of horn antenna	42 GHz; 150 μW/cm^2; 20 min (single exposure), 20 min/d for 5 or 20 successive days, before or after immunization	No effect of single exposure or five repeat exposures. Daily exposure for 20 d before immunization with SRBC resulted in significant reductions in thymic and renal cellularity	Lushnikov *et al.* (2001)
C57BL/6 mice	900 MHz (GSM); whole-body average SAR, 2 W/kg; 2 h/d for 4 wk	No changes in frequencies of various B cell types or in IgM/IgG serum levels. Production of IgM/IgG by B cells from exposed mice, challenged *in vitro* with lipopolysaccharides, was comparable to that in controls	Nasta *et al.* (2006)
NMRI mice	1.8–81.5 GHz; 1 μW/cm^2; 5 h	Increased production of TNF in peritoneal macrophages and splenic T lymphocytes. Increased mitogenic response in T lymphocytes.	Novoselova & Fesenko (1998), Novoselova *et al.* (1999)
NMRI mice	8.15–18 GHz; 1 μW/cm^2; 5 h –7 d	Increased NK cell activity, which persisted up to 24 h after exposure. Increased TNF production in peritoneal macrophages and splenic T lymphocytes after exposures of 5 h – 3 d, and reduced TNF production in peritoneal macrophages after an exposure of 7 d.	Fesenko *et al.* (1999b)
Rats [strain not given]	2450 MHz PW; SAR, 0.15–0.4 W/kg; 25 mo	Transient increase in the number of B and T lymphocytes and their response to the mitogen PHA after exposure for 13 mo	Guy *et al.* (1985)
Sprague-Dawley rats	900 MHz (GSM); SAR, 0.075 and 0.27 W/kg; 2h/d for 10 d	No alterations in the surface phenotype of splenic lymphocytes or in their concavalin A-stimulated mitogenic activity	Chagnaud & Veyret (1999)
Belgian White rabbits	2.1 GHz; 5 mW/cm^2; 3 h/d, 6 d/wk for 3 mo	Suppression of T-lymphocyte numbers at 2 mo; stronger response of T-cell-mediated immunity (delayed-type hypersensitivity response)	Nageswari *et al.* (1991)

AM, amplitude modulation; CW, continuous wave; d, day; GSM, Global System for Mobile Communications; h, hour; LPS, lipopolysaccharides; min, minute; mo, month; MW, microwave; NK, natural killer; PHA, phytohaemagglutinin; PFC, plaque-forming cells; PW, pulsed-wave; TNF, tumour necrosis factor; wk, week.

and female BALB/c mice. The time-averaged power density was 100 μW/cm^2, with a SAR of 0.14 ± 0.02 W/kg. Exposure to RF radiation as CW or AM (3 hours per day for 6 days) induced a non-significant increase in the number of antibody-producing cells in the spleen of male mice. No effects were seen in female mice.

Novoselova & Fesenko (1998) and Novoselova *et al.* (1999) exposed male NMRI mice to RF radiation at 8150–18 000 MHz (power density, 1 μW/cm^2) for 5 hours, and observed a significantly enhanced ($P < 0.05$) production of TNF in peritoneal macrophages and in T-cells in the spleen, and an increased mitogenic response in T lymphocytes.

Male NMRI mice received whole-body exposure to RF radiation at 10 GHz (average power density, 1 μW/cm^2) for different time periods (1 hour to 7 days). A significant enhancement of the production of tumour necrosis factor (TNF) in peritoneal macrophages and in splenic T lymphocytes was seen after exposures of 5–72 hours. Prolonged irradiation after 72 hours resulted in a decrease in production of TNF. In mice exposed to RF radiation at 8.15–18 GHz (average power density, 1 μW/cm^2) for 24 hours, TNF production in T-cells and macrophages was significantly increased ($P < 0.05$); in the latter cell type, this increase persisted for 3 days after termination of exposure (Fesenko *et al.*, 1999b).

Lushnikov *et al.* (2001) exposed male NMRI mice to RF radiation at 42.0 GHz (energy-flux density, 150 μW/cm^2) for 20 minutes per day, on five or twenty successive days before immunization with sheep erythrocytes, or for 20 minutes per day during five successive days after immunization. The response was estimated on day 5 after immunization by the number of antibody-forming splenic cells and by antibody titres. Humoral immunity and cellularity of the lymphoid organs did not change significantly after the single exposure, or after the series of five exposures before and after immunization. However, after daily exposure for 20 days before immunization, statistically significant reductions ($P < 0.05$) of thymic and splenic cellularity were observed.

Kolomytseva *et al.* (2002) exposed mice to RF radiation at 4200 MHz (power density, 150 μW/cm^2) for 20 minutes. The phagocytic activity of neutrophils was suppressed by about 50% in the 2–3 hours after a single exposure. The effect persisted for 1 day, and phagocytic activity then returned to normal within 3 days. A significant modification of the leukocyte profile in mice exposed for 5 days was observed after cessation of exposure: the number of leukocytes increased, mostly due to an increase in lymphocyte content.

Gatta *et al.* (2003) exposed C57BL/6 mice to GSM-modulated RF radiation at 900 MHz (SAR, 1 or 2 W/kg) for 2 hours per day for 1, 2 or 4 weeks. The number of spleen cells, the percentage of B and T-cells, and the distribution of T-cell subpopulations (CD4 and CD8) were not affected by the exposure. There was no difference in stimulation of T or B lymphocytes with specific monoclonal antibodies or lipopolysaccharides (LPS) between sham-exposed and exposed mice. After 1 week of exposure at a SAR of 1 or 2 W/kg, there was an increase in the production of interferon-gamma (IFN-γ), which was no longer observed when exposure was prolonged to 2 or 4 weeks.

Nasta *et al.* (2006) examined the effects of GSM-modulated RF radiation at 900 MHz (average SAR, 2 W/kg) on peripheral differentiation of B-cells and antibody production in female C57BL/6 mice exposed *in vivo*. Whole-body exposure for 2 hours per day, for 4 weeks, did not affect the frequencies of T1 and T2 B-cells, or of mature follicular B-cells and marginal zone B-cells in the spleen. Serum concentrations of IgM and IgG were not significantly affected. B-cells from mice exposed to RF radiation, which were then challenged *in vitro* with lipopolysaccharide (LPS) produced comparable amounts of IgM and IgG. Exposure to RF radiation did not alter the

ongoing antigen-specific immune response in immunized mice.

(b) Rat

In a study with rats receiving lifelong exposure to pulsed-wave RF radiation at 2450 MHz (SAR, 0.15–0.4 W/kg), Guy *et al.* (1985) found a significant increase in the number of splenic B and T lymphocytes at 13 months, but this effect had disappeared by the end of the study at 25 months. The exposed rats also showed a significant increase in their response to LPS and pokeweed mitogen after 13 months of exposure (no data available at 25 months).

Chagnaud & Veyret (1999) examined the effects of exposure to GSM-modulated RF radiation at 900 MHz (55 and 200 μW/cm^2; SAR, 0.075 and 0.279 W/kg; repetition rate, 217 Hz) for 2 hours per day for 10 days, on lymphocyte subpopulations in female Sprague-Dawley rats. The mitogenic response of the exposed rats was analysed by flow cytometry and a colorimetric method. No alterations were found in cell-surface markers (CD4, CD8 and IaAg) of splenic lymphocytes of exposed rats, or in their mitogenic activity when stimulated with concanavalin A.

(c) Rabbit

Nageswari *et al.* (1991) exposed male Belgian White rabbits to RF radiation at 2100 MHz (power density, 5 mW/cm^2; calculated average SAR, 0.83 W/kg) for 3 hours per day, 6 days per week, for 3 months, in specially designed miniature anechoic chambers. One group of rabbits was tested for T-lymphocyte-mediated cellular immune-response, being initially sensitized with bacille Calmette–Guérin (BCG) vaccine and challenged with tuberculin after termination of exposure. A second group was assessed for B-lymphocyte-mediated humoral immune-response. Samples of peripheral blood were collected each month during exposure or sham exposure and during follow-up at 5 and 14 days after termination of exposure (second group only). Significant suppression of numbers of T lymphocytes was noted in the exposed rabbits at 2 months and during the follow-up period. Rabbits in the group initially sensitized with BCG showed an increase in foot-pad thickness, which is indicative of a good T-lymphocyte-mediated immune response (a delayed-type hypersensitivity response).

[The Working Group noted that the available evidence from the numerous experimental studies *in vivo* that have assessed the effects of short-term and prolonged low-level exposure to RF radiation on the function and status of the immune system, clearly indicates that various shifts in the number and/or activity of immunocompetent cells can be detected. However, results have been inconsistent between experiments, despite comparable exposure conditions at similar intensities and radiation parameters. Short-term exposure to weak RF fields may temporarily stimulate certain humoral or cellular immune functions, while prolonged irradiation inhibits the same functions. The relevance of these observations to carcinogenicity was unclear.]

4.2.3 *Immunotropic effects of exposure to RF radiation in experimental systems: studies in human cells* in vitro

See Table 4.9

Cleary *et al.* (1990) studied human peripheral blood cells that were sham-exposed or exposed *in vitro* to RF radiation at 27 MHz (SAR, 0–196 W/kg) or 2450 MHz (SAR, 0–50 W/kg) for 2 hours under isothermal conditions (37 ± 0.2 °C). Immediately after exposure, peripheral blood mononuclear cells were isolated by Ficoll density-gradient centrifugation and cultured for 3 days at 37 °C with or without mitogenic stimulation by PHA. Lymphocyte proliferation was assayed at the end of the culture period by a 6-hour pulse-labelling with [^{3}H]thymidine. Exposure to radiation at

Table 4.9 Immunotropic effects of exposure to radiofrequency radiation in experimental systems *in vitro*

Experimental system	Exposure conditions	Results	Reference
Mouse PBMC; assessment of IL-2-dependent cytolytic T-lymphocyte proliferation (CTLL-2)	2450 MHz, CW (SAR, 5–50 W/kg) or PW (SAR, 5 W/kg), for 2 h	Statistically significant reduction in CTLL-2 proliferation after CW-RF radiation at low IL-2 levels and at SAR ≥ 25 W/kg; increase after PW-RF radiation	Cleary *et al.* (1996)
Rat basophilic leukaemia RBL-2H3 cells (a mast cell line)	835 MHz; 81 W/m^2; 3 × 20 min/d for 7 d	From day 4 onwards, the rates of DNA synthesis and cell replication continued to increase in exposed cells, but decreased in controls; cell morphology was also altered	Donnellan *et al.* (1997)
Human PBMC, microculture with mitogen (PHA) stimulation	27 MHz (SAR, 0–196 W/kg) or 2450 MHz (SAR, 0–50 W/kg); isothermal conditions (37 ± 0.2 °C); 2 h	Dose-dependent, statistically significant increase in [^{3}H] thymidine uptake in PHA-activated or unstimulated lymphocytes at SAR < 50 W/kg; uptake was suppressed at SAR ≥ 50 W/kg	Cleary *et al.* (1990)
Human lymphocytes; transformation of PBMC exposed to RF radiation or heated conventionally	2450 MHz CW or PW, at non-heating (37 °C) and various heating levels (temperaturę increases of 0.5, 1.0, 1.5, and 2 °C); SARs up to 12.3 W/kg	Both conventional and CW heating enhanced cell transformation to the same extent, which was correlated with the increase in incubation temperature. Exposure to PW RF radiation enhanced transformation at non-heating conditions.	Czerska *et al.* (1992)
Human mast cell line, HMC-1	864.3 MHz; average SAR, 7 W/kg; 3x20 min/d for 7 d	Effect on localization of protein kinase C (migration towards the cell membrane), upregution of *c-kit*, down-regulation of *NDPK*-beta, and the apoptosis-associated gene *DAD-1*.	Harvey & French (1999)
Human PBMC, microculture with mitogens, assessment of interleukin release, T-cell suppression (SAT)	1300 MHz PW; SAR, 0.18 W/kg; 1 h	Decreased spontaneous incorporation of [^{3}H]thymidine; no change in response to PHA or concanavalin A; no change in SAT index and saturation of IL-2 receptors; production of IL-10 by lymphocytes increased. Pulse-modulated MWs have immunotropic effects.	Dąbrowski *et al.* (2003)
Human lymphocytes; analysis of CD25, CD95, CD28 antigens in unstimulated and stimulated CD4+ or CD8+ T-cells from PBMC	1800 MHz (10 min on, 20 min off); SAR, 2 W/kg; 44 h. Microculture with or without antibody anti-CD3 mitogenic stimulation	No significant difference in proportion of cell subsets between exposed and sham-exposed lymphocytes from young or elderly donors. Slight but significant downregulation of CD95 expression in stimulated CD4+ T lymphocytes from elderly (average age, 88 yr) but not from younger (average age, 26 yr) donors.	Capri *et al.* (2006)

Table 4.9 (continued)

Experimental system	Exposure conditions	Results	Reference
Human PBMC, microculture with mitogens, assessment of interleukin (IL) release, T-cell suppression (SAT)	900 MHz (GSM); SAR, 0.024 W/kg; 15 min	Significantly increased response to mitogens and enhanced immunogenic activity of monocytes (LM index). The results suggest that immune activity of responding lymphocytes and monocytes can be enhanced by 900 MHz MW.	Stankiewicz *et al.* (2006)
Human PBMC, microculture with mitogens, assessment of several immune functions	1950 MHz (GSM; 5 min on, 10 min off); SAR, 1 W/kg; 8 h	No effects of RF radiation on immune functions: (i) the intracellular production of IL-2 and INF-γ in lymphocytes, and IL-1 and TNF-α in monocytes; (ii) the activity of immune-relevant genes (IL 1-α and β, IL-2, IL-2-receptor, IL-4, MCSF-receptor, TNF-α, TNF-α-receptor); or (iii) the cytotoxicity of lymphokine-activated killer cells (LAK cells) against a tumour cell line.	Tuschl *et al.* (2006)

d, day; h, hour; IL-2, interleukin 2; IL-10, interleukin 10; INF-γ, interferon γ; LM, lymphocytes-monocytes; MCSF, macrophage colony-stimulating factor; MW, microwave; min, minute; mo, month; NDPK, nucleoside diphosphate kinase; PBMC, peripheral blood mononuclear cells; PHA, phytohaemagglutinin; PW, pulsed-wave; SAR, specific absorption rate; SAT index, a measure of the suppressive activity of T cells; TNF, tumour necrosis factor; yr, year

either frequency at SARs < 50 W/kg resulted in a dose-dependent, statistically significant increase in [^{3}H]thymidine uptake in PHA-activated or non-stimulated lymphocytes. Exposure at SARs of ≥ 50 W/kg suppressed [^{3}H]thymidine uptake. There were no detectable effects of RF radiation on lymphocyte morphology or viability.

Czerska *et al.* (1992) determined the effects of continuous- and pulsed-wave RF radiation at 2450 MHz (average SARs up to 12.3 W/kg) on spontaneous lymphoblastoid transformation of human lymphocytes *in vitro*. Peripheral blood mononuclear cells from healthy donors were exposed for 5 days to conventional heating, or to continuous- or pulsed-wave RF radiation at 2450 MHz under non-heating (37 °C) or various heating conditions (temperature increases of 0.5, 1.0, 1.5, or 2 °C). The pulsed exposures involved pulse-repetition frequencies from 100 to 1000 pulses per second at the same average SARs as the continuous exposures. At the end of the incubation period, spontaneous lymphoblastoid-cell transformation was detected by use of an image-analysis system. At non-heating levels, continuous-wave exposure did not affect transformation compared with sham-exposed cultures. Under heating conditions, both conventional heating and exposure to continuous-wave RF radiation enhanced transformation to the same extent, and correlated with the increases in incubation temperature. Exposure to pulsed-wave RF radiation enhanced transformation under non-heating conditions. At heating levels, it enhanced transformation to a greater extent than did conventional heating or continuous-wave exposure. The results indicate that pulsed-wave RF radiation at 2450 MHz had a different action on the process of lymphoblastoid cell transformation *in vitro* than continuous-wave radiation at 2450 MHz and at the same average SARs.

Human HMC-1 mast cells were exposed to RF radiation at 846.3 MHz (average SAR, 7.3 W/kg) for 20 minutes, three times per day (at 4-hour intervals) for 7 days. During the 20 minutes of exposure, the cells were outside the incubator and the temperature in the cell-culture medium dropped to 26.5 °C. Effects were seen on the localization of protein kinase C (migration to the cell membrane), and on expression of three genes: the proto-oncogene *c-kit* (upregulated 36%), the gene encoding transcription factor nucleoside diphosphate kinase B (downregulated 38%), and the apoptosis-associated gene *DAD-1* (downregulated 47%) (Harvey & French, 1999).

Dąbrowski *et al.* (2003) exposed peripheral blood mononuclear cells from healthy donors (n = 16) to pulse-modulated RF radiation at 1300 MHz (power density, 1 mW/cm^2; SAR, 0.18 W/kg) for 1 hour. This exposure decreased the spontaneous incorporation of [^{3}H]thymidine, but the proliferative response of lymphocytes to PHA and concavalin A, the T-cell suppressive activity (SAT index), and the saturation of IL-2 receptors did not change. The IL-10 production by the lymphocytes increased (P < 0.001), and the concentration of interferon-gamma (IFNγ) remained unchanged or slightly decreased in the culture supernatants. Exposure to RF radiation modulated monokine production by monocytes. The production of IL-lβ increased significantly, the concentration of its antagonist (IL-lra) dropped by half and the concentration of tumour necrosis factor α (TNF-α) remained unchanged. These changes in monokine proportion (IL-lβ versus IL-lra) resulted in a significant increase in the immunogenic activity of the monocytes, *i.e.* the influence of monokines on the lymphocyte mitogenic response, which reflects the activation of monocyte immunogenic function. The results indicated that pulse-modulated microwaves have the potential to influence immune function, stimulating preferentially the immunogenic and pro-inflammatory activity of monocytes at relatively low levels of exposure.

Capri *et al.* (2006) analysed CD25, CD95, CD28 molecules in non-stimulated and stimulated CD4+ or CD8+ T-cells *in vitro*. Peripheral

blood mononuclear cells from 10 young (age, 26 ± 5 years) and 8 elderly (age, 88 ± 2 years) donors were sham-exposed or exposed to intermittent (10 minutes on, 20 minutes off) RF radiation at 1800 MHz (SAR, 2 W/kg) for 44 hours, with or without mitogenic stimulation. No significant changes in the percentage of these subsets of cells were found between exposed and sham-exposed non-stimulated lymphocytes in young or elderly donors. A small, but statistically significant downregulation of CD95 expression was noted in stimulated CD4+ T lymphocytes from elderly, but not from younger donors, after exposure to RF radiation.

Stankiewicz *et al.* (2006) investigated whether cultured human immune cells induced into the active phases of the cell cycle (G1, S) were sensitive to exposure to RF radiation at 900 MHz (GSM; 27 V/m; SAR, 0.024 W/kg) for 15 minutes. The exposed microcultures of peripheral blood mononuclear cells showed a significantly higher proliferative response to PHA or concanavalin A, a stronger response to mitogens, and a higher immunogenic activity of monocytes than sham-exposed control cultures.

Tuschl *et al.* (2006) exposed peripheral blood mononuclear cells to RF radiation at 1950 MHz, with a SAR of 1 W/kg, in an intermittent mode (5 minutes on, 10 minutes off) for 8 hours. Numerous immune parameters were evaluated, including: intracellular production of IL-2 and INFγ in lymphocytes, and IL-1 and TNF-α in monocytes; activity of immune-relevant cytokines (IL 1-α and β, IL-2, IL-2-receptor, IL-4, macrophage colony-stimulating factor (MCSF)-receptor, TNF-α, TNF-α-receptor); and cytotoxicity of lymphokine-activated killer cells (LAK cells) against a tumour cell line. For each parameter, blood samples from at least 15 donors were evaluated. No statistically significant effects of exposure were found.

[The Working Group concluded that exposure *in vitro* to non-thermal intensities of RF radiation provided weak evidence for effects on immunocompetent cells.]

4.3 Effects of exposure to RF radiation on gene and protein expression

4.3.1 Gene expression

(a) Humans

There were no studies examining gene or protein expression after exposure to RF radiation in humans.

(b) Experimental animals

See Table 4.10

(i) Caenorhabditis elegans

No effect was found on the transgene expression of *hsp16* (encoding heat-shock protein hsp16, the equivalent of human hsp27) in the nematode *C. elegans* – transgenic for *hsp16* – exposed to continuous-wave or pulsed-wave RF radiation at 1.8 GHz (SAR, 1.8 W/kg) for 2.5 hours at 25 °C (Dawe *et al.*, 2008). In a second study, *C. elegans* was exposed to continuous-wave RF radiation at 1 GHz (SAR, 0.9–3 mW/kg; power input, 0.5 W) for 2.5 hours at 26 °C. In this exposure set-up, with very low SAR, the difference in temperature between exposed and sham-exposed samples did not exceed 0.1 °C. In a gene-expression array, no statistically significant effects on the gene-expression pattern were found (Dawe *et al.*, 2009). [The Working Group noted that experiments at these low SAR levels may favour a no-effect outcome.]

(ii) Drosophila melanogaster

Using a semiquantitative reverse-transcriptase polymerase chain reaction (RT–PCR), Lee *et al.* (2008) showed that exposure of fruit flies (*D. melanogaster*) to RF radiation at 835 MHz (SAR, 1.6 or 4.0 W/kg) for up to 36 hours (resulting in 90% or 10% survival, respectively, at low and high SAR) affected the

Table 4.10 Effects on gene expression in animal models after exposure to radiofrequency radiation *in vivo*

Biological model	Exposure conditions	Assessment of gene expression	Results	Comments	Reference
Caenorhabditis elegans (strain PC72)	1800 MHz (GSM); CW or DTX; SAR, 1.8 W/kg; 2.5 h at 25 °C	Stress-inducible reporter gene β-galactosidase under control of *hsp16* heat-shock promoter, measured as β-galactosidase activity	No effect on expression of *hsp16*		Dawe *et al.* (2008)
Caenorhabditis elegans wild-type (N2)	1000 MHz (CW); SAR, 0.9–3 mW/kg; 2.5 h	Affymetrix *C. elegans* Genome GeneChip array (> 22 000 probes)	21 upregulated and 6 downregulated genes; less than expected by chance		Dawe *et al.* (2009)
Drosophila melanogaster F, age 3 d	835 MHz; SAR, 1.6 and 4.0 W/kg; 12, 18, 24, 30, 36 h	Semi-quantitative RT-PCR; analysis of stress genes *rolled* (*Erk*), *Jra* (*Jun*), *Dfos* (*Fos*) and apoptosis-related genes: *Bcl2, Dmp53* (*Tp53*), *reaper, hid*	Increased expression of *rolled* (1.6 W/kg) and *Jra* and *Dfos* (4.0 W/kg); protein-expression changes confirmed gene-expression changes; increased expression of *Bcl2* (1.6 W/kg) and *Dmp53, reaper, hid* (4.0 W/kg)		Lee *et al.* (2008)
Mouse brain (BALB/cJ) age, 5–6 wk	800 MHz (GSM); SAR, 1.1 W/kg (whole-body); SAR, 0.2 W/kg (brain); 1 h	Affymetrix Mouse Expression Array 430A (22 600 probe sets)	Filtering microarray results for fold-changes > 1.5 and > 2.0 provided; respectively 301 and 30 differentially expressed probe sets	No consistent evidence of modulation of gene expression in whole brain	Paparini *et al.* (2008)
Rat brain (Wistar, M)	900 MHz (GSM); SAR, 0.3 or 1.5 W/kg; 900 MHz (CW), SAR, 7.5 W/kg; 4 h	Gene expression assessed immediately after exposure. Hybridization *in situ*; *hsp70, c-fos, c-jun, GFAP;* optical-density analysis	*hsp70* mRNA: increase at 7.5 W/kg (CW); *c-fos* mRNA: increase at all exposures; *c-jun* mRNA: decline at 1.5 W/kg (GSM) and 7.5 W/kg (CW). *GFAP* mRNA: no effect	Exposure by use of a mobile phone	Fritze *et al.* (1997a)
Rat brain (F344)	1600 MHz; SAR, 0.16, 1.6, 5 W/kg; 2 h	Northern blot for ornithine decarboxylase, *Fos* and *Jun* in total brain RNA; normalization to α-actin probe	No effect on mRNA expression		Stagg *et al.* (2001)
Rat brain (F344)	915 MHz GSM (DTX); average whole-body SAR, 0.4 W/kg; 2 h	Affymetrix U34A GeneChip (8800 genes)	11 upregulated genes; 1 downregulated gene		Belyaev *et al.* (2006)

Table 4.10 (continued)

Biological model	Exposure conditions	Assessment of gene expression	Results	Comments	Reference
Rat brain (F344)	1800 MHz (GSM); whole-body SAR, 0.013 W/kg (brain SAR, 0.03 W/kg); 6 h	Affymetrix rat 2302 chip (31 099 genes); categories: upregulated > 1.05-fold; downregulated < 0.95-fold; unaffected, 0.95–1.05-fold	Numerous upregulated and downregulated genes in nearly all 4956 gene ontologies analysed, especially regulatory genes of membrane integrity and cell signalling.	Less reliable due to small "fold-change" criteria; information on affected genes not given	Nittby *et al.* (2008)
Rat brain, facial nerves (Sprague-Dawley)	1.9 GHz (GSM); SAR, 0.9, 1.18, 1.8 W/kg; 6 h/d, for 126 d	RT-PCR analysis of mRNA for calcium ATPase, N-CAM, NGF-B, VEGF in brain and in facial nerves	Statistically significant upregulation of all mRNAs	Radiation source was a mobile phone; less reliable dosimetry	Yan et al. (2008, 2009)
Rat (newborn) kidney (pregnant Sprague-Dawley rats)	9.4 GHz (GSM); SAR, 0.5 mW/kg; continuously on days 1–3 or 4–7 after mating	RT-PCR analysis of mRNA expression of bone morphogenetic proteins (Bmp) and their receptors (Bmpr)	Increased mRNA expression of Bmp4 and Bmpr1a, and decreased expression of Bmpr2 in kidneys of newborns from rats exposed on days 1–3 or 4–7 of gestation. No effect on expression of Bmp7.	These changes may reflect a delay in renal development	Pyrpasopoulou *et al.* (2004)

CW, continuous wave; d, day; DTX, discontinuous transmission mode; GSM, Global System for Mobile communication; h, hour; N-CAM, neural cell-adhesion molecule; NGF, neural growth factor; RT-PCR, reverse-transcriptase polymerase chain reaction; SAR, specific absorption rate; VEGF, vascular endothelial growth factor; wk, week

expression of genes encoding stress-response kinases and proteins involved in the regulation of apoptosis. Interestingly, some of these genes – involved in cell-survival signalling pathways – responded to the lower SAR, while others – involved in apoptotic pathways – were activated by the higher SAR. The changes in gene expression were followed by similar changes in expression of the corresponding proteins (Table 4.11), which strengthens the validity of the findings.

(iii) Mouse

Paparini *et al.* (2008) exposed BALB/cJ mice to RF radiation at 1800 MHz (whole-body SAR, 1.1 W/kg; brain-averaged SAR, 0.2 W/kg) for 1 hour, and analysed gene expression in total brain homogenate. The array analysis did not show any significant modulation of gene expression in the exposed mice compared with sham-exposed controls. Under less stringent conditions, 42 genes were found to be upregulated, while 33 were downregulated. However, these results could not be confirmed with RT–PCR. [The Working Group noted that analysing mRNA from a whole-brain homogenate might obscure the detection of any effect in specific brain regions.]

(iv) Rat

Groups of 30 male Wistar rats were exposed to RF radiation at 900 MHz (GSM; brain-averaged SAR, 0.3 or 1.5 W/kg) or to continuous-wave RF radiation at 900 MHz (brain-averaged SAR, 7.5 W/kg), for 4 hours. To mimick actual life exposure as closely as possible, the signal was generated with a commercial mobile GSM phone, and a telephone conversation was simulated by repeatedly playing the first half of H. von Kleist's comedy *Der zerbrochene Krug* (Von Kleist, 1811). Subgroups of 10 rats were processed immediately after exposure, or 24 hours or 7 days later. Enhanced expression of Hsp70 mRNA was observed in the brain at the higher SAR of 7.5 W/kg, and a small but significant increase was seen in c-Fos expression in the brain at the two lower SAR values (Fritze *et al.*, 1997a). [The Secretariat was pleased to learn that the spoken text to which the rats were exposed in this study mimicked actual life exposure of the authors, but was uncertain about confounding effects on the rat brain.]

Fischer 344 rats were exposed to RF radiation at 1600 MHz (brain-averaged SAR, 0.16, 1.6, and 5.0 W/kg) for 2 hours. No changes were seen in core body temperature and corticosterone or adrenocorticotrophic hormone levels in the brain that could be attributed to exposure to RF radiation. Also the levels of *Odc*, *Fos* and *Jun* mRNA in brain tissue showed no differences with sham-exposed controls that could be ascribed to RF radiation (Stagg *et al.*, 2001).

Three groups of pregnant Wistar rats were sham-exposed, or exposed to pulsed-wave RF radiation at 9.4 GHz (SAR, 0.5 mW/kg) continuously during days 1–3 after mating, or during days 4–7 after mating, respectively. In 20–26 newborns collected from each of these groups, significantly altered expression and localization of proteins involved in bone morphogenesis were observed in the kidney. These changes may reflect a delay in renal development (Pyrpasopoulou *et al.*, 2004).

Whole-body exposure of Fischer 344 rats to RF radiation at 915 MHz (GSM; SAR, 0.4 W/kg) for 2 hours led to significantly ($P < 0.0025$) increased expression (1.34–2.74-fold) of eleven genes and reduced expression (0.48-fold) of one gene in the cerebellum of the exposed rats. Only these genes showed significantly increased/decreased expression in all nine comparisons between three exposed and three sham-exposed rats (Belyaev *et al.*, 2006).

Nittby *et al.* (2008) reported a strong response and changes in the expression of numerous genes after whole-body exposure of Fischer 344 rats to RF radiation at 1800 MHz (GSM; SAR, 13 mW/kg) for 6 hours. In this study, changes in gene expression were considered when expression

Table 4.11 Effects on protein expression in human and animal models after exposure to radiofrequency radiation *in vivo*

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Human skin, female volunteers	900 MHz (GSM); SAR, 1.3 W/kg; local exposure, 1 h; punch-biopsies collected immediately after exposure	Protein expression by 2DE-based proteomics	Expression was significantly increased for 7 proteins, reduced for 1; 2 proteins – one up, one down – were affected in all 10 volunteers	Proteins not identified	Karinen *et al.* (2008)
Drosophila melanogaster	1900 MHz (GSM); SAR, 1.4 W/kg ; 2 × 1 h per day for 10 d	Immunocytochemistry; serum response element (SRE)-binding, ELK1 phosphorylation, hsp70	Increase in expression of all measured proteins	Unreliable dosimetry: exposure by placing vials next to mobile-phone antenna; unreliable data analysis, single experiments; no statistical analysis	Weisbrot *et al.* (2003)
Drosophila melanogaster	835 MHz; SAR, 1.6 and 4.0 W/kg; 12, 18, 24, 30, 36 h	Immunocytochemistry; phospho-JNK, phospho-ERK, phospho-p38MAPK	Activation of ERK (at SAR 1.6 W/kg), activation of JNK (at SAR 4.0 W/kg); no effect on p38MAPK		Lee *et al.* (2008)
Drosophila melanogaster	900 MHz; SAR 0.64 W/kg; continuous/intermittent exposure	Immunofluorescence; phalloidin detection of actin stress fibres	Increase in disorganization of actin network	Unreliable dosimetry: exposure by placing vials next to mobile-phone antenna	Chavdoula *et al.* (2010)
Mouse brain (C57BL/6NTac) age, 8 wk	900 MHz (GSM); SAR, 4 W/kg. Mice were restrained for 1 h during exposure; brains perfusion-fixed immediately after exposure	Immunocytochemistry; c-fos	Non-significant decline (~50%) in c-fos expression in exposed cingulate cortex; no effects in other parts of the brain	Significant difference of exposed/sham-exposed with cage-controls; effects may be due to immobilization	Finnie (2005)
Fetal mouse brain (BALB/c)	900 MHz (GSM); SAR, 4 W/kg; 1 h daily, on days 1–19 of gestation. Mice were restrained during exposure	Immunocytochemistry; c-fos	Average expression of cfos was non-significantly increased in basal ganglion and reduced in pyriform cortex		Finnie *et al.* (2006a)
Mouse brain (C57BL/6NTac)	900 MHz (GSM); SAR, 4 W/kg; 1 h/d, 5 d/wk, 104 wk. Mice were restrained during exposure	Immunocytochemistry; c-fos	No effects on c-fos expression, but no numerical analysis shown	No statistical details given. Significant difference of exposed/sham-exposed with cage-controls; effects may be due to immobilization	Finnie *et al.* (2007)

Table 4.11 (continued)

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Fetal mouse brain (BALB/c)	900 MHz (GSM); SAR, 4 W/kg; 1 h daily on days 1–19 of gestation. Mice were restrained during exposure	Immunocytochemistry; Hsp25, Hsp32, Hsp70	No effect on expression of Hsp; no numerical analysis shown	No statistical details given; shown only examples of stained brain slices	Finnie *et al.* 2009a
Mouse brain [strain NS]	900 MHz (GSM); SAR, 4.0 W/kg; 1 h single exposure or 1 h/d, 5 d/wk, 104 wk	Immunocytochemistry; aquaporin (AQP4, marker of blood–brain barrier function)	No effect on aquaporin expression; no numerical analysis shown	No statistical details given; shown only examples of stained brain slices	Finnie *et al.* (2009b)
Mouse brain [strain NS]	900 MHz (GSM); SAR, 4.0 W/kg; 1 h single exposure or 1 h/d, 5 d/wk, 104 wk	Immunocytochemistry; ionized calcium-binding adaptor molecule Iba1 (microglia activation marker)	No effect on Iba1 expression		Finnie *et al.* (2010)
Transgenic mouse (hsp70.1-deficient)	849 MHz or 1763 MHz; whole-body average SAR, 0.04 W/kg; 2 × 45 min/d with 15-min interval, 5 d/wk, for up to 10 wk; mice killed after 4, 8, 10 wk of exposure	Immunocytochemistry: PCNA Western blot: actin, HSP90, HSP70, HSP25, ERK and phospho-ERK, JNK and phospho JNK, p38MAPK and phospho-p38MAPK	No effect on HSP90, HSP70, HSP25 expression No effect on phosphorylation of ERK, JNK and p38MAPK		Lee *et al.* (2005)
Mouse brain (C57BL/6N)	849 MHz or 1763 MHz; brain average SAR, 7.8 W/kg; 1 h/d, 5 d/wk, for 6 or 12 mo	Immunocytochemistry: PCNA, GFAP, NeuN	No effect on expression of PCNA, GFAP, NeuN	No numerical data, no statistical details given Visual evaluation only	Kim *et al.* (2008b)
Mouse brain (ICR, M)	835 MHz; SAR, 1.6 and 4.0 W/kg; whole-body exposure; 5 h (single), 1 h/d for 5 d; daily [no time given] for 1 mo (1.6 W/kg only)	Immunocytochemistry: calbindin, calretinin	Changes in expression of calbindin and calretinin after 1 mo exposure, particularly in the inner molecular layer of the dentate gyrus of the brain	Alterations in calcium-binding proteins affect cellular Ca^{2+} levels and hippocampal functions associated with neuronal connectivity and integration	Maskey *et al.* (2010)
Rat brain (Wistar, M)	900 MHz (GSM, SAR 0.3 and 1.5 W/kg; CW, SAR 7.5 W/kg CW); 4 h; protein expression examined 24 h after exposure	Immunocytochemistry; c-fos, fos B, c-jun, jun B, jun D, krox-20, krox-24, Hsp70, Gfap, MHCclass II;	No effect on expression of any of the proteins examined	Exposure by use of a mobile telephone; only visual inspection and evaluation of samples; no statistical details	Fritze *et al.* (1997a)

Table 4.11 (continued)

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Rat brain (F344, M)	915 MHz (GSM, DTX); average whole-body SAR, 0.4 W/kg; 2 h	Western blot: Hsp70	No effect on expression of hsp70 protein		Belyaev *et al.* (2006)
Rat brain (Wistar albino)	900 MHz (GSM); SAR, 2.0 W/kg; 2 h/d, 7 d/wk, for 10 mo	Immunocytochemistry: caspase-3, Tp53	No effect on Tp53; caspase-3 re-localized to nucleus	Protein expression scored by visual inspection and evaluation	Dasdag *et al.* (2009)
Rat brain (Sprague-Dawley)	900 MHz (GSM); SAR, 6 and 1.5 W/kg; exposure 15 min/d for 7 d at high SAR, and 45 min/d for 7 d at low SAR	Cytochrome-*c* oxidase activity in brain slices by staining with di-amino-benzidine and horse-heart cytochrome-*c* as substrate	Decreased cytochrome-*c* oxidase activity in prefrontal, frontal and posterior cortex, septum, and hippocampus, at SAR 6 W/kg	Exposure may affect brain metabolism and neuronal activity	Ammari *et al.* (2008)
Rat brain (Sprague-Dawley)	900 MHz (GSM); SAR, 6 and 1.5 W/kg; exposure 15 min/d for 8 wk at high SAR, and 45 min/d for 8 wk at low SAR; samples taken 3 and 10 d after exposure	Immunocytochemistry: glial fibrillary acidic protein (Gfap)	Increase in Gfap expression	Gfap increase may be a sign of gliosis	Ammari *et al.* (2010)
Rat skin (hairless rat, F)	900 MHz or 1800 MHz (GSM); local skin SAR, 5 W/kg; 2 h; sampling immediately after exposure	Immunocytochemistry: Ki67, filaggrin, collagen, elastin	No effect on number of cells expressing Ki-67; no effect on density of filaggrin, collagen and elastin		Masuda *et al.* (2006)
Rat skin (hairless rat)	900 MHz or 1800 MHz (GSM); local skin SAR, 2.5 and 5 W/kg; 2 h/d, 5 d/wk, for 12 wk; samples taken 72 h after the last exposure	Immunocytochemistry: Ki67, filaggrin, collagen, elastin	No effect on number of cells expressing Ki-67, no effect on density of filaggrin, collagen and elastin		Sanchez *et al.* (2006a)
Rat skin (hairless rat)	900 MHz or 1800 MHz (GSM); local skin SAR, 5 W/kg; 2 h; sampling immediately after exposure. Multiple exposures to 900 MHz or 1800 MHz (GSM); local skin SAR, 2.5 or 5 W/kg; 2 h/d, 5 d/wk, for 12 wk; samples taken 72 h after the last exposure	Immunocytochemistry: Hsc70, Hsp70 and Hsp25	No effect on expression of stress proteins	Analysis of three areas on three photographs per stained skin slice, quantified by image-analysis software	Sanchez *et al.* (2008)

Table 4.11 (continued)

Biological model	Exposure conditions	Assessment of protein expression	Results	Comments	Reference
Rat kidney (Wistar; newborn)	9.4 GHz; 5 μW/cm^2; 0.5 mW/kg; continuously exposed on days 1–3 or 4–7 after mating	Kidneys from newborns of exposed rats were investigated by means of immunocytochemistry (Bmp4 and Bmp7) and *in situ* hybridization (receptors Bmpr2and Bmpr1a)	Significant increase in expression and change in localization of Bmp4 Increase in Bmpr1a, decrease in Bmpr2 expression. Effects were stronger after exposure *in utero* on days 1–3 of gestation (embryogenesis) than on days 4–7 (organogenesis)	Effects dependent on timing of exposure *in utero*	Pyrpasopoulou *et al.* (2004)
Rat thyroid (Wistar)	900 MHz (GSM); SAR, 1.35 W/kg; 20 min/d, 3 wk	Immunocytochemistry, transmission electron microscopy; Casp3 and Casp9 (markers of apoptosis)	Significant increase in expression of Casp3 and Casp9; thyroid hypertrophy; reduced thyroid-hormone secretion; formation of apoptotic bodies	Histomorphometry of thyroid tissue	Eşmekaya *et al.* (2010)
Rat testis (Sprague-Dawley)	848.5 MHz (CDMA signal); SAR, 2.0 W/kg; 2 × 45 min/d with a 15-min interval; 12 wk	Western blot; p21, Tp53, Bcl2, Casp3, PARP	No effect for Tp53, Bcl2, Casp3; no result given for PARP or p21		Lee *et al.* (2010)

2DE, two-dimensional gel electrophoresis; CDMA, code division multiple access; d, day; DTX, discontinuous transmission mode; F, female; GSM, Global System for Mobile Communications; h, hour; M, male; min, minute; mo, month; NS, not specified; SAR, specific absorption rate; wk, week

had risen or declined by 5%, compared with controls. [The genes investigated in this study were not identified, and the changes in gene expression were not validated by RT–PCR.]

Sprague-Dawley rats were exposed to RF radiation at 1.9 GHz (with SARs of 0.9, 1.18, or 1.8 W/kg at a distance of 2.2 cm) from a mobile phone operating in three different modes, for 2 × 3 hours per day, for 18 weeks. A statistically significant upregulation of the mRNAs for calcium ATPase, neural cell-adhesion molecule, neural growth factor, and vascular endothelial growth factor was measured in the brain of these rats. In addition, these mRNAs were upregulated in the mandibular and buccal branches of the facial nerve. These results suggest that neurological damage may be associated with long-term mobile-phone use (Yan *et al.*, 2008, 2009).

4.3.2 Protein expression

See Table 4.11

(a) Humans

In a pilot study, a small skin area of one forearm of 10 volunteers was exposed to RF radiation at 900 MHz (GSM; SAR, 1.3 W/kg) for 1 hour. Immediately after exposure, punch biopsies were taken from the exposed area and from the other non-exposed forearm of the same person. Proteins were extracted and analysed by means of 2D-gel electrophoresis. Changes in the expression of eight proteins were found; two of these proteins were observed in all 10 volunteers. Identity and function of these proteins were not given (Karinen *et al.*, 2008).

(b) Experimental animals

(i) Drosophila melanogaster

Exposure of fruit flies (*D. melanogaster*) to RF radiation at 1900 MHz from a mobile phone (GSM; SAR, 1.4 W/kg) for 2 × 1 hour per day, for 10 days, resulted in an increase of 3.6–3.9-fold in the expression of heat-shock protein hsp70, the phosphorylation of ELK1 kinase, and the DNA-binding activity of the serum-response element (SRE) (Weisbrot *et al.*, 2003).

As indicated above, exposure of *D. melanogaster* to RF radiation at 835 MHz (GSM; SAR, 1.6 or 4.0 W/kg) for up to 36 hours affected the expression of genes encoding stress-response kinases and proteins involved in the regulation of apoptosis. The expression of the corresponding proteins was confirmed by Western blotting with protein-specific antibodies (Lee *et al.*, 2008).

Chavdoula *et al.* (2010) exposed *D. melanogaster* to continuous or intermittent RF radiation at 900 MHz (GSM) from a digital mobile phone (SAR, 0.64 W/kg) for 6 minutes per day, for 6 days. The phone was fully charged and its antenna was in contact with the glass vials containing the flies, and parallel to the vial axis. Exposure to RF radiation caused an increased disorganization of the actin network of the egg chambers. This effect was due to DNA fragmentation, as measured with the TUNEL assay.

(ii) Mouse

Nine studies were performed in mice on changes in protein expression after exposure to RF radiation. The mice were of different age (fetus, or adults aged 6–8 weeks) and different strains (C57BL/6N, C57BL/6NTac, hsp70.1-deficient, BALB/c, ICR); mouse strain and age were not specified in two studies (Finnie *et al.*, 2009b, 2010). Changes in protein expression were assessed by use of immunocytochemistry with monoclonal and polyclonal antibodies.

ICR mice were exposed to RF radiation at 835 MHz (SAR, 1.6 W/kg and 4.0 W/kg) for 5 hours, 1 hour per day for 5 days, or for 1 month. Changes in the expression of the calcium-binding proteins calbindin D28-k (CB) and calretinin (CR) were measured in the hippocampus by use of immunohistochemistry. Exposure for 1 month produced almost complete loss of pyramidal cells in the CA1 area of the brain. These alterations in calcium-binding proteins may cause

changes in cellular Ca^{2+} levels, which could affect hippocampal functions associated with neuronal connectivity and integration (Maskey *et al.*, 2010).

Six of the published studies came from a single research group. Most of these studies were based on the same biological material that was separately stained to detect different proteins. Studies from this group have reported no effects on the expression of the following proteins after exposure to RF radiation: c-Fos in adult and fetal mouse brain, stress proteins Hsp25, Hsp32, and Hsp70 in fetal brain, aquaporin 4 in adult brain, and ionized calcium-binding adaptor molecule Iba1 in brain [age not given]. Others have reported similar findings (see Table 4.11). [The Working Group noted that these studies generally provided very few numerical and technical details.]

(iii) Rat

Eleven studies were performed with rats of different ages (newborn to adult) and different strains (Wistar, Fisher 344, hairless rat, Sprague-Dawley). In addition, different tissues were examined (brain, skin, kidney, testis, thyroid). Detection of changes in protein expression was mostly by immunocytochemistry with protein-specific monoclonal and polyclonal antibodies, and in some studies by Western blotting.

Five studies assessed the effects of exposure to RF radiation in rat brain (Fritze *et al.*, 1997a; Belyaev *et al.*, 2006; Dasdag *et al.*, 2009; Ammari *et al.*, 2008, 2010). These studies considered a limited number of proteins, generally gave negative results for changes in expression, and provided limited statistical detail. Samples were often analysed visually and without calculating statistical significance. For this reason the results were considered less reliable (see comments in Table 4.11).

In three studies, the effects of mobile-phone radiation on the skin of hairless rats were investigated (Masuda *et al.*, 2006; Sanchez *et al.*, 2006a, 2008). No effects were observed on any of the proteins analysed.

Pyrpasopoulou *et al.* (2004) used immunocytochemistry and hybridization in situ to examine the effects of exposure to RF radiation on kidneys of newborn rats and found that exposure affected the expression of bone morphogenic protein (Bmp4) and bone morphogenic protein receptors (Bmpr2, Bmpr1a). Similar changes were observed in the expression of the corresponding genes, as noted above (Section 4.3.1).

Eşmekaya *et al.* (2010) observed increased expression and activity of the apoptosis-regulating proteins caspase 3 (Casp3) and caspase 9 (Casp9) by use of light microscopy, electron microscopy, and immunohistochemical methods in the thyroid of Wistar rats exposed to RF radiation at 900 MHz (SAR, 1.35 W/kg) for 20 minutes per day, for 3 weeks.

Lee *et al.* (2010) examined the effects on rat testis of exposure to RF radiation at 848.5 MHz (SAR, 2.0 W/kg) twice per day for 45 minutes, 5 days per week, for 12 weeks. No significant effects were found on any of the apoptosis-associated proteins tested (p21, Tp53, Bcl2, Casp3, PARP).

[The Working Group noted that only few studies in experimental animals have examined the effects of RF radiation on gene and protein expression. These studies used a variety of biological models, and had mixed and inconsistent results. Many proteins that are known to be important for the initiation and development of cancer in humans were not evaluated. The Working Group concluded that the available studies on gene and protein expression in humans and animals exposed to RF radiation did not provide evidence to support mechanisms of carcinogenesis in humans.]

(c) In-vitro studies in human cells

(i) Heat-shock proteins

See Table 4.12

Heat-shock proteins (HSPs) are a highly conserved family of chaperone proteins that are found in all cell types; they are expressed abundantly and have diverse functions. HSPs are expressed in response to cold, heat and other environmental stress factors, although some are expressed constitutively. HSPs increase heat tolerance and perform functions essential to cell survival under these conditions. Some HSPs serve to stabilize proteins in specific configurations, while others play a role in the folding and unfolding of proteins, acting as molecular chaperones. Stress-induced transcription of HSPs requires activation of heat-shock factors that bind to the heat-shock promoter element, thereby activating its transcription activity. Overexpression of HSPs has been linked to oncogenic development and poor prognostic outcome for multiple cancers, possibly through the roles of HSPs as mediators of signal transduction and inhibitors of oncogene-mediated senescence (Evans *et al.*, 2010). Since markedly increased expression of HSPs is co-incident with exposure of cells to a variety of stress factors, expression of HSP genes and proteins in response to exposure to RF radiation has been extensively investigated in a variety of cell models.

Since the effects of RF radiation on HSP expression have been reviewed previously (Cotgreave, 2005), only recent publications on this issue are reviewed in detail in this Volume. Several studies have reported changes in HSP expression in human cell lines exposed to RF radiation.

Tian *et al.* (2002) exposed human glioma (MO54) cells to RF radiation at 2.45 MHz (SAR, 5–100 W/kg) for up to 16 hours. An increase in HSP70 protein levels at SARs of 25 and 78 W/kg was observed, but no effect was seen at SARs below 20 W/kg. [The Working Group noted that thermal confounding cannot be ruled out in this study due to the high relative SARs tested, the highly non-uniform SAR distribution within the exposure system, and the considerable reduction in cell viability (~70%) in some samples during exposure.]

Leszczynski *et al.* (2002) exposed a human endothelial cell line (EA.hy926) to RF radiation at 900 MHz (GSM; SAR, 2 W/kg) for 1 hour. The phosphorylation status of several proteins was altered. Specifically, HSP27 was found to undergo a transient increase in expression and phosphorylation immediately after exposure, but this effect had disappeared at 1 or 4 hours after exposure.

Lim *et al.* (2005) exposed human peripheral blood cells to RF radiation at 900 MHz (average SAR, 0.4, 2.0 or 3.6 W/kg) for 20 minutes, 1 hour, or 4 hours. No statistically significant differences were detected in the number of lymphocytes or monocytes expressing stress proteins HSP27 or HSP70 after exposure, compared with the numbers in sham-exposed samples.

Miyakoshi *et al.* (2005) exposed human malignant glioma MO54 cells to RF radiation at 1950 MHz (SAR, 1, 2, or 10 W/kg) for up to 2 hours. Exposed cells did not show increased expression of HSP27 or HSP70 protein, but levels of phosphorylated HSP27 had decreased significantly in cells exposed at a SAR of 10 W/kg for 1 or 2 hours.

The transcription of HSPs is regulated by the DNA-binding activity of heat-shock transcription factors (HSFs). These factors bind to specific regulatory elements in the promoter region of HSP genes. In a study by Laszlo *et al.* (2005), no DNA-binding activity of HSF protein was detected in hamster (HA-1), mouse (C3H 10T½) and human cells (HeLa S3) exposed to 835.62 MHz (SAR, ~0.6 W/kg) or 847.74 MHz (SAR, ~5 W/kg) RF radiation, for up to 24 hours.

Lee *et al.* (2006) observed no detectable alterations in the expression of HSP27, HSP70 or HSP90 transcripts after exposure of human T-lymphocyte Jurkat cells to RF radiation at 1763 MHz (SAR, 2 or 20 W/kg) for 30 minutes or 1 hour.

Table 4.12 Effects on heat-shock proteins in human cell lines exposed to radiofrequency radiation *in vitro*

Tissue/cell line	Exposure conditions	End-point and target	Results	Comments	Reference
MO54 glioma cells	2450 MHz, CW; SARs, 5, 20, 50, 100 W/kg; 2, 4, 8, 16 h	HSP70 protein expression	Increased expression of HSP70 only at SARs > 20 W/kg	SAR values very high; thermal confounding possible	Tian *et al.* (2002)
EA.hy926 endothelial cells	900 MHz (GSM); SAR, ~2 W/kg; 1 h	p-HSP27 protein level	Transient change in p-HSP27 and phosphorylation of other unidentified proteins; transient change in HSP27 protein level	Effect had disappeared at 1 or 4 hours after exposure	Leszczynski *et al.* (2002)
EA.hy926 endothelial cells	1800 MHz (GSM); SAR, 2.0 W/kg; 1 h	Protein HSP27 expression	No effect		Nylund *et al.* (2009)
Human lens epithelial cells (hLEC)	1800 MHz (GSM); SAR, 1, 2, 3 W/kg; 2 h	HSP70 mRNA and protein expression	Increased expression of HSP70 protein at SAR 2 and 3 W/kg; no change in mRNA levels		Lixia *et al.* (2006)
HeLa, S3 and EA.hy296 cell lines	837 MHz (TDMA); SAR, 5 W/kg; 1, 2, 24 h; or 900 MHz (GSM); SAR, 3.7 W/kg; for 1, 2, 5 h	p-HSP27 protein levels	No effect		Vanderwaal *et al.* (2006)
A172 cells and IMR-90 fibroblasts	2142.5 MHz (CW or W-CDMA); SAR, 0.08 and 0.8 W/kg; 2–48 h	HSP27, HSP40, HSP70, HSP105 mRNA and protein expression, p-HSP27 protein levels	No effect		Hirose *et al.* (2007)
Human blood	900 MHz (CW or GSM); SAR, 0.4, 2 or 3.6 W/kg; 20 min, 1 h, or 4 h	HSP27, HSP70 protein expression	No effect		Lim *et al.* (2005)
A172 cells	2450 MHz (CW); SAR, 5–200 W/kg; 1–3 h	HSP27, HSP70 protein expression; p-HSP27 protein levels	No effect	SAR values very high (thermal confounding possible)	Wang *et al.* (2006)
MO54 cells	1950 MHz (CW); SARs, 1, 2, 10 W/kg; 1 or 2 h	HSP27, HSP70 protein expression; p-HSP27 protein levels	Decrease in p-HSP27 at highest SAR		Miyakoshi *et al.* (2005)
Mono Mac 6 cells	1800 MHz (CW and GSM); SAR, 2 W/kg; 1 h	HSP70 protein expression	No effect		Simkó *et al.* (2006)
Mono Mac 6 and K562 cells	1800 MHz (CW and GSM); SARs, 0.5, 1, 1.5, or 2 W/kg; 45 min	HSP70 protein expression	No effect		Lantow *et al.* (2006a)
U-251MG cells	6000 MHz (CW) ; power density 5.4 μW/cm^2 or 0.54 mW/cm^2; 1–33 h	HSP70 mRNA and protein	No effect		Zhadobov *et al.* (2007)

Table 4.12 (continued)

Tissue/cell line	Exposure conditions	End-point and target	Results	Comments	Reference
HTR-8/ neo; human trophoblast cell line	1817 MHz (GSM); SAR, 2.0 W/kg; 1 h	HSP70, HSC70 mRNA expression	No effect		Valbonesi *et al.* (2008)
Human keratinocytes, fibroblasts and reconstructed epidermis	900 MHz (GSM); SAR, 2 W/kg; 48 h	HSP27, HSC70, and HSP70 protein expression	Keratinocytes: no effect Epidermis: slight but significant increase in HSP70 Fibroblasts: significant decrease in HSC70		Sanchez *et al.* (2006b)
Human primary keratinocytes and fibroblasts	1800 MHz (GSM); SAR, 2 W/kg; 48 h	HSP27, HSP70 and HSC70 protein expression	No effect		Sanchez *et al.* (2007)
HeLa S3, HA-1, C3H 10T½	835 MHz (FDMA) and 847 MHz (CDMA); SAR, 0.6 W/kg (low dose) and 5 W/kg (high dose); 5–60 min, 24 h	HSF protein DNA-binding activity	No effect		Laszlo *et al.* (2005)
Jurkat cells	1763 MHz (CDMA), SAR, 2 or 20 W/kg; 30 min or 1 h	HSP27, HSP70, HSP90 protein expression	No effect		Lee *et al.* (2006)
MO54, A172 and T98 cell lines	1950 MHz (CW); SAR, 1 or 10 W/kg; 1 h	HSP27 mRNA and protein expression, p-HSP27 protein levels	No effect on HSP27 expression Slight decrease in p-HSP27 levels in MO54 cells		Ding *et al.* (2009)
TK6 cells	1900 MHz (pulsed-wave; 5 min on, 10 min off); SAR, 1 and 10 W/kg; 6 h	HSP27, HSP70 mRNA expression	No effect		Chauhan *et al.* (2006a)
HL60 and Mono Mac 6 cells	1900 MHz (pulse-wave; 5 min on, 10 min off); SAR, 1 and 10 W/kg; 6 h	HSP27, HSP70 mRNA expression	No effect		Chauhan *et al.* (2006b)
Mono Mac 6 and U87MG cells	1900 MHz (pulsed-wave; 5 min on, 10 min off); SAR, 0.1, 1 and 10 W/kg; 6–24 h	HSP27, HSP40, HSP70, HSP90, HSP105 mRNA expression	No effect		Chauhan *et al.* (2007a)
U87MG cells	1900 MHz; SAR, 0.1, 1, 10 W/kg; 4 h	HSP27, HSP40, HSP70, HSP86, HSP105 mRNA expression	No effect		Qutob *et al.* (2006)

CDMA, code-division multiple access; CW, continuous wave; FDMA, frequency-domain multiple access; GSM, Global System for Mobile Communications; h, hour; HSC, heat-shock cognate; HSF, heat-shock factor; HSP, heat-shock protein; p-HSP27, phosphorylated-HSP27; min, minute; RF, radiofrequency; SAR, specific absorption rate; SRE, serum-response element; TDMA, time-domain multiple access; WCDMA, wideband code-division multiple access

Lixia *et al.* (2006) exposed human lens epithelial cells to RF radiation at 1800 MHz (GSM; SAR, 1, 2, or 3 W/kg) for 2 hours. The authors noted increased expression of HSP70 protein at the higher SARs, but no corresponding change was observed in mRNA expression.

Simkó *et al.* (2006) exposed a human monocyte-derived cell line (Mono-Mac-6) to RF radiation at 1800 MHz (SAR, 2 W/kg) for 1 hour, either alone or with ultra-fine particles. The authors observed no effect on the expression of HSP70 protein. In a follow-up study, Lantow *et al.* (2006a) investigated whether exposure to RF radiation at 1800 MHz (SAR, 0.5–2.0 W/kg) for 45 minutes had an effect on expression of HSP70 in Mono-Mac-6 and K562 cells. No significant effects of exposure to RF radiation were detected in the expression of HSP70 protein in either cell line under any of the conditions tested.

Vanderwaal *et al.* (2006) found no evidence of altered HSP27 phosphorylation in three human cell lines (HeLa, S3 and EA.hy296) after exposure to RF radiation at 837 MHz (SAR, 5.0 W/kg) for 1, 2, or 24 hours, or at 900 MHz (SAR, 3.7 W/kg) for 1, 2 or 5 hours.

Wang *et al.* (2006) did not detect any alterations in HSP27, HSP70 or expression of phosphorylated-HSP27 protein in human A172 cells – derived from a malignant glioblastoma – exposed to RF radiation at 2450 MHz (SARs of up to 50 W/kg) for 0–3 hours.

Sanchez *et al.* (2006b) evaluated possible stress-related effects in isolated human skin cells and in reconstructed human epidermis exposed to RF radiation at 900 MHz (SAR, 2 W/kg) for 48 hours. Immunohistochemical analysis did not reveal any detectable changes in expression of HSP27 or inducible HSP70 in exposed keratinocytes. However, levels of HSC70 (heat shock cognate) protein were significantly decreased in dermal fibroblasts isolated from human skin after exposure to RF radiation. Such results were not seen in reconstructed human epidermis. Human skin cells may thus react to exposure by modulating the expression of some HSPs, but this response may depend on the cell model. In a follow-up study, the same investigators found that primary human skin cells (keratinocytes and fibroblasts) did not display any alterations in inducible HSP27, HSP70 or HSC70 protein levels after exposure at 1800 MHz (SAR, 2 W/kg) for 48 hours (Sanchez *et al.*, 2007). [The authors did not discuss the different responses observed in these two studies.]

Hirose *et al.* (2007) examined HSP27 phosphorylation, gene and protein expression in human glioblastoma A172 cells and human IMR-90 fetal lung fibroblasts exposed to RF radiation at 2142.5 MHz (SARs up to 0.8 W/kg) for 2–48 hours. No evidence of altered HSP27 phosphorylation or increased mRNA expression of a variety of HSPs was found in either cell line.

Zhadobov *et al.* (2007) investigated the expression of stress-sensitive genes and proteins in a human glial cell line (U-251MG) exposed to RF radiation at 60 GHz (power density, 5.4 μW/cm^2 or 0.54 mW/cm^2) for 1–33 hours. No evidence was found for altered expression of stress-response genes, as determined by reporter assays and RT-PCR. Western-blot analysis indicated no effects of RF radiation on levels of clusterin or HSP70 protein.

Valbonesi *et al.* (2008) observed no change in expression of HSP70 in the human HTR-8/SVneo trophoblast cell-line exposed to RF radiation at 1800 MHz (SAR, 2 W/kg) for 1 hour.

Exposure of the human endothelial cell line EA.hy926 to 1.8 GHz RF radiation (SAR, 2.0 W/kg) for 1 hour did not result in altered HSP protein expression; phosphorylation status was not assessed in this study (Nylund *et al.*, 2009).

Ding *et al.* (2009) studied three human glioma cell-lines (MO54, A172, T98) and found no evidence of altered HSP expression or phosphorylation after exposure to RF radiation at 1950 MHz (SAR, 1 or 10 W/kg) for 1 hour. These findings were supported by results of a series of earlier studies by Chauhan *et al.* (2006a, b, 2007a)

and Qutob *et al.* (2006), in which exposure at 1900 MHz (SAR, 0.1–10 W/kg) for 4–24 hours did not alter the transcript expression of HSP27, HSP40, HSP70, HSP90 or HSP105, in several human cell lines (MM6, U87MG, HL60, TK6).

[The Working Group noted that a small number of studies reported altered expression of HSPs in certain cell lines (Leszczynski *et al.*, 2002; Tian *et al.*, 2002; Miyakoshi *et al.*, 2005; Lixia *et al.*, 2006; Sanchez *et al.*, 2006b). However, it was not clear whether these responses were specific to the cell line, the frequency, the modulation or model used, or were false-positives, e.g. artefacts caused by irregularities in the exposure system. The majority of studies conducted in cultured human cells to date have found no evidence that exposure to RF radiation under non-thermal conditions elicits alterations in the expression of HSP genes or proteins.]

(ii) Proto-oncogenes and signal-transduction pathways

See Table 4.13

Several studies have investigated the ability of RF radiation to mediate the expression of proto-oncogenes and proteins involved in the regulation of signal-transduction pathways. Proto-oncogenes are genes with the capacity to induce cellular proliferation and/or transformation. While these genes are constitutively expressed at low levels, they are rapidly and transiently induced in response to external stress stimuli. Similarly, transcriptional activity in response to stress factors can be mediated by mitogen-activated protein kinase (MAPK) pathways, which include the extracellular signal-regulated kinase (ERK), p38 and the c-Jun N-terminal kinase (JNK) cascades. These pathways are complex and regulate a variety of cellular processes, including proliferation, differentiation, metabolism and the stress response. Upon phosphorylation of these kinases, a large number of regulatory proteins and transcription factors can become activated, thereby altering cellular processes and allowing further gene transcription.

Li *et al.* (1999) exposed human fibroblasts to continuous-wave RF radiation at 837 MHz (SAR, 0.9–9.0 W/kg) for 2 hours. No evidence of altered expression of TP53 protein was found.

Leszczynski *et al.* (2002) exposed a human endothelial cell line (EA.hy926) to RF radiation at 900 MHz (SAR, 2 W/kg) for 1 hour. A transient increase was noted in p38-MAPK and in phosphorylation of HSP27. This effect could be inhibited by SB203580 (a specific inhibitor of p38-MAPK). Since accurate measurements indicated no alterations in cell-culture temperature during the exposure period, activation of the p38-MAPK stress-response pathway might be a potential mode of non-thermal molecular interaction of RF radiation with biological tissue.

Caraglia *et al.* (2005) exposed human epidermoid-cancer KB cells to RF radiation at 1950 MHz (SAR, 3.6 W/kg) for 1–3 hours. Decreased expression was noted for the proteins Ras, Raf-1 and Akt. The activity of Ras and ERK1/2 was determined by their phosphorylation status, and found to be reduced. This exposure to RF radiation increased JNK1/2 activity and expression of HSP27 and HSP70, but caused a reduction in p38-MAPK activity and HSP90 expression. [The Working Group noted that details on the exposure system were incompletely described, and that these observations may have been due to thermal effects.]

Miyakoshi *et al.* (2005) exposed human glioma cells (MO54) to RF radiation at 1950 MHz (SAR, 10 W/kg) for 2 hours. A decrease was noted in the phosphorylation of HSP27 at serine-78, indicating repression of the p38-MAPK cascade or activation of an HSP27 phosphatase.

Lee *et al.* (2006) exposed Jurkat cells to RF radiation at 1763 MHz (SAR, 2 or 20 W/kg) for 30 minutes to 1 hour in the presence or absence of the phorbol-ester, 12-*O*-tetradecanoylphorbol-13-acetate (TPA). There was no evidence of an altered phosphorylation status of ERK1/2,

Table 4.13 Studies on the effect of radiofrequency radiation on the expression of proto-oncogenes in human cells *in vitro*

Tissue/cell line	Exposure	End-point and target	Results	Comments	Reference
Human endothelial EA.hy926 cells	900 MHz (GSM); ~2 W/kg; 1 h	p38MAPK protein expression	Transient change		Leszczynski *et al.* (2002)
Rat1, HeLa cells	800/875/950 MHz; power density 0.07–0.31 mW/cm^2; 5–30 min	ERK1/2, JNK1/2, p38MAPK, EGFR, Hb-EGF protein expression, phosphorylation status	Transient increase of ERK1/2 phosphorylation at 0.10 mW/cm^2. Phosphorylation of p38MAPK and JNK1/2 (stress-activated cascades) is not changed. Phosphorylation is ROS-dependent	Stress-activated cascades are not affected, which may indicate that effects are non-thermal. Temperature remained constant within 0.05 °C.	Friedman *et al.* (2007)
Human epidermoid KB cell line	1950 MHz; SAR, 3.6 W/kg; 1, 2, 3 h	Ras, Raf-1, Akt, ERK1/2, JNK1/2, HSP27, HSP70, HSP90 protein expression, phosphorylation status	Expression of ras, Raf-1, Akt, and HSP90 was reduced; expression of HSP27 and HSP70 was increased. Phosphorylation of ERK1/2, ras, p38MAPK was reduced, while that of JNK1/2 was increased	Incomplete details on RF exposure; no temperature control; possible thermal confounding	Caraglia *et al.* (2005)
Human neuroblastoma (SH-SY5Y) cells	900 MHz (GSM); SAR, 1 W/kg; 5, 15, 30 min, 6 h, 24 h	EGR1, ERK1/2, SAPK/JNK, p38MAPK, ELK1, BCL2, survivin mRNA and protein expression, phosphorylation status	Transient increase in EGR1 and ELK1 transcript levels; transient increase in ERK1/2, SAPK/JNK phosphorylation. Evidence of apoptosis after 24 h exposure	Confounding due to environmental factors unclear	Buttiglione *et al.* (2007)
Jurkat cells	1763 MHz (CDMA); SAR, 2 or 20 W/kg; 30 min or 1 h	p38MAPK, ERK1/2, JNK1/2 protein expression, phosphorylation status	No effect on protein expression for HSP90, HSP70, HSP27; no effect on phosphorylation with/without TPA	Exposure conditions and temperature properly controlled	Lee *et al.* (2006)
Human glioma MO54 cells	1950 MHz (CW); SAR, 10 W/kg; 1h and 2h	Phosphorylated HSP27 protein levels	Decrease in phosphorylation of HSP27		Miyakoshi *et al.* (2005)
TK6, MM6, HL-60 cells	1900 MHz (PW; 5 min on, 5 min off); SAR, 1 or 10 W/kg; 6 h	c-fos, c-myc, c-jun mRNA expression	No effect		Chauhan et al. (2006a, b)
WS1neo human foreskin fibroblasts	837 MHz (CW); SAR, 0.9 or 9 W/kg; 2 h	TP53 protein expression	No effect		Li *et al.* (1999)
Human glioblastoma A172, human lung IMR-90 fibroblasts	2142.5 MHz (CW, W-CDMA); SAR, 80, 250, 800 mW/kg; 24, 28, 48 h	APAF1, TP53, TP53BP2 and CASP9 protein levels, phosphorylation status	No effect	Temperature control unclear	Hirose *et al.* (2006)

CDMA, code-division multiple access; CW, continuous-wave; FDMA, frequency-division multiple access; FMCW, frequency-modulated continuous wave; GSM, Global System for Mobile communications; h, hour; min, minute; RF, radiofrequency; SAR, specific absorption rate; TDMA, time-division multiple access; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; W-CDMA, wideband code-division multiple access

JNK1/2 or p38-MAPK after exposure to RF radiation, with or without TPA.

Chauhan *et al.* (2006a, b) exposed three human-derived cell lines (TK6, MM6, HL-60) to intermittent (5 minutes on/10 minutes off) RF radiation at 1900 MHz (SAR, 1 or 10 W/kg) for 6–24 hours. No significant differences were observed in relative expression levels of the proto-oncogenes c-*JUN*, c-*FOS* and c-*MYC* in any of the cell lines examined.

Hirose *et al.* (2006) examined gene-transcript levels in human A172 and IMR-90 cells following exposure to RF radiation. A series of genes known to be involved in TP53-mediated apoptosis (including *APAF1*, *TP53*, *TP53BP2* and *CASP9*) were assessed after the cells had been exposed at 2142.5 MHz (SAR, 0.08–0.8 mW/kg) for up to 48 hours. No significant differences were observed in the expression of these TP53-related apoptosis genes, relative to the sham-exposed control groups, under any of the conditions tested.

Buttiglione *et al.* (2007) assessed the expression levels of several transcription factors (EGR1, BCL2, ELK1) downstream of the MAPK pathways. EGR1 transcript expression and phosphorylation of ERK1/2 and JNK in human SH-SY5Y neuroblastoma cells were evaluated after exposure to 900 MHz RF radiation (SAR, 1 W/kg) for 5 minutes up to 24 hours. There was a transient increase in EGR1 levels at 5–30 minutes after exposure; this effect was no longer evident at 6–24 hours after exposure. Phosphorylation of ERK1/2, JNK1/2 and ELK1 was also transiently increased after various exposure times (5 minutes to 6 hours), while a significant decrease in the transcript levels of BCL2 and survivin was observed after 24 hours of exposure. However, a significant decrease in cell viability (as determined by the MTT assay) was noted, as well as the appearance of subG$_1$ nuclei and a G$_2$–M block (as determined by flow cytometry) after 24 hours of exposure. [The Working Group noted that the appearance of subG$_1$ nuclei is indicative of possible induction of apoptosis in the cell culture. It was unclear whether this effect was thermal or non-thermal in nature.]

Friedman *et al.* (2007) reported that low-level exposure of serum-starved HeLa cells to RF radiation at 875–950 MHz (power densities, 0.07–0.31 mW/cm^2) for 5–30 minutes, significantly activated the ERK1/2 signal-transduction pathway via generation of ROS through NADPH-oxidase activation. Neither the p38-MAPK nor the JNK1/2 stress-response pathways were activated by RF radiation. [The Working Group noted that the description of the exposure conditions in this study was poor.]

[The Working Group noted that there was weak evidence from studies with human cell lines that non-thermal RF exposure could result in alterations in the expression or phosphorylation of proto-oncogenes or proteins involved in signal-transduction pathways. Most studies that report altered expression of genes or proteins, or phosphorylation of proteins involved in cell homeostasis, proliferation and signal-transduction pathways, appeared to have been conducted under unique exposure conditions, with results that show no clear dose– and time–response.]

(d) High-throughput studies of gene and protein expression

See Table 4.14

In recent years, many studies have employed high-throughput techniques to analyse differential gene/protein expression in human cells in response to exposure to RF (reviewed by Vanderstraeten & Verschaeve, 2008; McNamee & Chauhan, 2009). While such technology offers ample opportunity for understanding potential biological interactions of RF radiation in a hypothesis-free testing approach, it is also subject to generating a large number of "false-positive" results. For this reason, it is fundamentally important that such high-throughput studies employ rigorous statistical-inference analysis, include an appropriate number of biological replicates, and validate the differential expression of gene

Table 4.14 High-throughput studies on the effects of radiofrequency radiation on gene and protein expression

Tissue/cell line	Exposure	Platform	Results	Comments	Reference
C3H 10T½ mouse cells	847.7 MHz (CDMA) or 835.6 MHz (FDMA); SAR, 5 W/kg; 24 h	Affymetrix GeneChip U74Av2	Differential expression of ~200 genes	Not confirmed by RT-PCR	Whitehead *et al.* (2006)
Mouse embryo primary cultured neurons/ astrocytes	1900 MHz (GSM); SAR not reported; 2 h	GEArray Q Series Mouse Apoptosis gene array, RT-PCR	Neurons: upregulation of *Casp2*, *Casp6*, *Pycard*; *Casp9* and *Bax* mRNA levels unchanged Astrocytes: upregulation of *Casp2*, *Casp6*, *Pycard*, *Bax*	Uncontrolled experimental conditions (exposure from mobile phone). Confirmed by RT-PCR	Zhao *et al.* (2007a)
Rat neurons	1800 MHz (GSM PW; 5 min on, 10 min off); SAR, 2 W/kg; 24 h	Affymetrix GeneChip Rat Neurobiology U34 Array	Of 1200 screened genes, 24 were upregulated and 10 were downregulated	Confirmed by RT-PCR; fair agreement with micro-array data	Zhao *et al.* (2007b)
EA.hy926 human endothelial cells	900 MHz (GSM); SAR, 2.4 W/kg; 1 h	2DE protein analysis (silver staining), MALDI-MS	Found 38 altered spots; 4 spots identified by MALDI-MS: 2 spots (increased expression) were identified as vimentin isoforms (confirmed by Western blot) 2 spots (downregulated expression) were identified as IDH3A and HNRNPH1		Nylund & Leszczynski (2004)
EA.hy926, EA.hy926v1,	900 MHz (GSM); SAR, 2.8 W/kg; 1 h	Atlas Human v1.2 cDNA arrays (1167 genes screened); 2DE protein analysis (silver staining)	EA.hy926 cells: 1 gene downregulated, 38 altered protein spots in EA.hy926 EA.hy926v1 cells: 13 genes upregulated, 45 altered protein spots	No confirmation of gene-expression results with RT-PCR, or of proteome results with Western blotting; minimum number of biological replicates	Nylund. & Leszczynski (2006)
MCF7 cells	849 MHz (CDMA); SAR, 2 or 10 W/kg; 1 h/d for 3 d	2DE protein analysis (silver staining), electrospray ionization MS-MS, Western blotting, RT-PCR	No reproducible changes in protein expression; GRP78 protein/RNA not differentially expressed	Exposure conditions and temperature properly controlled. Minimum number of biological replicates	Kim *et al.* (2010)
Human lens epithelial cells (hLEC)	1800 MHz (GSM); SAR, 1, 2, 3.5 W/kg; 2 h	2-DE protein analysis (silver staining), electrospray ionization MS-MS	More than 1600 protein spots were differentially expressed in each condition *vs* sham-exposed control. Of four upregulated proteins (at SAR 2 and 3.5 W/kg), two were identified by MS (hnRNP K, HSP70)	Number of independent experiments unclear; no confirmation by Western blotting	Li *et al.* (2007)

Table 4.14 (continued)

Tissue/cell line	Exposure	Platform	Results	Comments	Reference
Jurkat cells, fibroblasts, leukocytes	1800 MHz (GSM PW, 5 min on, 10 min off); SAR, 2 W/kg; 8 h	2DE protein analysis (fluorescence), ion-trap MS-MS	No differentially expressed protein spots by fluorescence 2DE. Increased rate (> 2-fold) of *de novo* protein synthesis in exposed cells	Not corrected for multiple comparisons; no confirmation by Western blotting; minimum number of biological replicates	Gerner *et al.* (2010)
NB69, U937 EA.hy926, CHME5, HL60, lymphocytes, used pooled RNA	900 or 1800 MHz (GSM); SAR, 0.77 or 1.8–2.5 W/kg; 1, 24, and 44 h	Human Unigene RZPD-2 cDNA array (~75 000 probes screened)	Differential gene expression in three cell lines (EA.hy926, U937, HL60)	No confirmation of results with RT-PCR; insufficient number of biological replicates. Exposure conditions and temperature properly controlled	Remondini *et al.* (2006)
Jurkat cells	1763 MHz (CDMA); SAR, 10 W/kg; 1 h/d for 3 d	Applied Biosystems 1700 full genome array (30000 probes)	No gene-expression changes > 2-fold; 10 genes changed > 1.3-fold ($P < 0.1$)	No confirmation of results with RT-PCR	Huang *et al.* (2008a)
A172, H4 and IMR90 cell lines	2142.5 MHz (CW and W-CDMA); SAR, 0.08, 0.25, 0.80 W/kg; 96 h	Affymetrix Human Genome HG-U133A and B arrays	Differential expression (>2-fold) of 8 genes (H4 cells), 5 genes (A172 cells) and 1 gene (IMR90 cells)	Genes not all identified; insufficient number of independent experiments; no confirmation by RT-PCR	Sekijima *et al.* (2010)
MCF7 cells	1800 MHz (GSM PW; 5 min on, 10 min off); SAR, 2 or 3.5 W/kg; 24 h	Affymetrix GeneChip Test3 arrays (~22 000 probes screened)	No effect at 2 W/kg; five genes upregulated at 3.5 W/kg	RT-PCR analysis did not confirm differential expression of the five candidate genes identified by microarray analysis. Insufficient number of biological replicates	Zeng *et al.* (2006)
A172 and IMR90 cells	2142.5 MHz (CW and W-CDMA); SAR, 0.08, 0.25, 0.8 W/kg; 24, 28, 48 h	Affymetrix Human Genome U133 Plus 2.0 GeneChip (38 000 probes screened)	No consistent changes in gene expression in two experiments. Lack of response for TP53-related gene expression (*TP53*, *TP53BP2*, *APAF1* and *CASP9*) confirmed by microarray hybridization and RT-PCR	Insufficient number of biological experiments	Hirose *et al.* (2006)
A172 cells and IMR90 fibroblasts	2142.5 MHz (CW and W-CDMA); SAR, 0.08 or 0.8 W/kg; 2–48 h	Affymetrix Human Genome U133 Plus 2.0 GeneChip (38 000 probes screened)	No effect	No parallel experiments with RT-PCR; insufficient number of biological replicates	Hirose *et al.* (2007)

Table 4.14 (continued)

Tissue/cell line	Exposure	Platform	Results	Comments	Reference
U87MG glioblastoma cells	1900 MHz (PW); SAR 0.1, 1, 10 W/kg; 4 h	Agilent Human 1A arrays (~22 000 probes screened)	No effect	Lack of effect on several HSPs confirmed by RT-PCR; multiple doses of RF radiation tested; concurrent positive, negative and sham controls; exposure conditions and temperature properly controlled	Qutob *et al.* (2006)
TK6, HL60, Mono Mac 6 cells	1900 MHz (pulsed-wave; 5 min on, 10 min off); SAR, 0.1, 1, 10 W/kg; 6 or 24 h	Agilent Human 1Av2 arrays (~22 000 probes screened)	No effect	No parallel experiments with RT-PCR; multiple doses of RF radiation tested; concurrent positive, negative and sham controls; exposure conditions and temperature properly controlled	Chauhan *et al.* (2007a)
Glial cell line (SVGp12)	2450 MHz (CW); SAR, 1, 5, 10 W/kg; 1, 2, 24 h	AceGene Premium Human DNA Array, RT-PCR	Microarray analysis identified 23 differentially expressed genes and showed 5 unassigned gene spots: 17 genes were upregulated, 11 were downregulated	RT-PCR analysis with 22 of the 23 genes did not confirm microarray data. Minimum number of biological replicates	Sakurai *et al.* (2011)
EA.hy926 cells	1800 MHz (GSM); SAR, 2 W/kg; 1 h	2DE protein analysis, MALDI-TOF MS analysis, Western blotting	Eight differentially expressed protein spots; three identified as SRM, GRP78 and PSA1	Western blot found no response in GRP78, or changes in HSP27 and vimentin expression	Nylund *et al.* (2009)
HUVEC, HBMEC cells	1800 MHz (GSM); SAR, 2 W/kg; 1 h	2DE-DIGE	No differentially expressed spots in either cell line when corrected for multiple comparisons (correction for false-discovery rate)	Exposure conditions and temperature properly controlled	Nylund *et al.* (2010)

2DE, two-dimensional gel electrophoresis; CDMA, code-domain multiple access; CW, continuous wave; d, day; DIGE, difference gel electrophoresis; FDMA, frequency domain multiple access; GSM, Global System for Mobile Communications; h, hour; HSC, heat-shock cognate; HSF, heat-shock factor; HSP, heat-shock protein; min, minute; MALDI-MS, matrix-assisted laser desorption/ionization mass spectrometry; MALDI-TOF MS, matrix-assisted laser desorption/ionization-time of flight mass spectrometry; MS-MS, tandem mass spectrometry; p-HSP27, phosphorylated-HSP27; PW, pulsed wave; RT-PCR, reverse-transcriptase polymerase chain reaction; SAR, specific absorption rate; SRE, serum response element; W-CDMA, wideband-code division multiple access

and proteins by use of alternative techniques (e.g. RT-PCR or Western blotting).

(i) Proteomics studies in human cells

Nylund & Leszczynski (2004) reported altered expression of 38 protein spots – observed in a two-dimensional (2D) electrophoresis gel – and identified 4 proteins by matrix-assisted laser desorption/ionization–mass spectrometry (MALDI-MS) in the human endothelial cell line EA.hy926, exposed to RF radiation at 900 MHz (SAR, 2.4 W/kg) for 1 hour. Of particular interest was that two of the spots identified were isoforms of the cytoskeletal protein, vimentin. In a subsequent genomics/proteomics study, Nylund & Leszczynski (2006) observed that 1 gene was downregulated in the EA.hy926 cell line and 13 genes were upregulated in a related EA.hy926v1 cell line exposed to RF radiation at 900 MHz (SAR, 2.8 W/kg) for 1 hour. Proteome analysis indicated 38 differentially expressed proteins in the EA.hy926 cell line and 45 altered proteins in the EA.hy926v1 cell line. The identity of the differentially expressed proteins was not determined. More recent studies by these authors, with exposure of the cells at 1800 MHz (SAR, 2.0 W/kg) did not show the altered expression of, e.g. vimentin (Nylund *et al.*, 2009, 2010). [The Working Group noted that the observations reported in these studies were either not confirmed by Western blotting, or were identified as artefacts upon further investigation. The discrepancy in the results with RF radiation at 900 and 1800 MHz may be attributable to the different exposure frequencies; the different distribution of SAR within the cell cultures, *i.e.* less uniform SAR distribution at 900 MHz; and the occurrence of false positives when using the silver-stain-based 2D gel-electrophoresis technique.]

Li *et al.* (2007) exposed human lens epithelial cells to RF radiation at 1800 MHz (SAR, 1, 2, and 3.5 W/Kg) for 2 hours. In the 2D-electrophoresis pattern, enhanced expression was noted of two stress-related proteins, namely HSP70 and ribonucleoprotein K. [The Working Group noted that failure to confirm the identity of the spots by Western blotting made the results of this study difficult to interpret.]

Kim *et al.* (2010) employed 2D gel-electrophoresis to examine the proteome of human MCF7 breast-cancer cells exposed to RF radiation at 849 MHz (SAR, 2 or 10 W/kg) for 1 hour per day, on three consecutive days. At 24 hours after exposure, no significant differences in protein expression were identified between exposed and sham-exposed cells.

Gerner *et al.* (2010) assessed relative protein expression in Jurkat cells, human fibroblasts and primary mononuclear cells (leukocytes) exposed to intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 2 W/kg during the "on" phase) for 8 hours, in growth medium containing [^{35}S]methionine/cysteine. No significant differences were observed between sham-exposed and RF-exposed samples in the expression of any particular proteins by use of 2D gel-electrophoresis with fluorescence detection. However, cells exposed to RF radiation for 8 hours displayed a significant increase in protein synthesis, measured as enhanced incorporation of ^{35}S in autoradiographs of the 2D gel: in Jurkat cells, 14 proteins showed a doubling of the spot intensity in the autoradiograph. All these proteins were identified by ion-trap mass spectrometry. Of these 14 proteins, 13 were also enhanced in 2D autoradiographs prepared with samples from exposed fibroblasts. Several stress-responsive proteins were particularly affected, including Hsp70 and Hsp90. The enhancement of the signals in the leukocytes (stimulated/non-stimulated) were much weaker, with only heat-shock protein Hsp60 showing a more than twofold increase. These results suggest increased synthesis de novo of these proteins in cells exposed to RF radiation. None of these observations were validated with other techniques.

[The Working Group noted that the studies assessing proteomic changes in human cells

were limited in number, and shortcomings were evident in some.]

(ii) Transcriptomics studies in human cells

Remondini *et al.* (2006) isolated RNA from six human-derived cell lines (NB69, EA.hy926, T lymphocytes, U937, CHME5, and HL-60) after exposure to RF radiation at 900 MHz or 1800 MHz (SAR, 1.0, 1.3, 1.4, 1.8–2.5, and 2.0) for 1, 2, or 44 hours. In some cases, the exposure at 1800 MHz was intermittent with 5/5, 5/10, or 10/20 minutes on/off. Total RNA was isolated and processed for transcriptome analysis, i.e. to detect changes in gene expression. There was no evidence of differential gene expression in three of the cell lines tested (NB69, T lymphocytes, CHME5), but alterations in gene expression (12–34 differentially expressed genes) were observed in EA.hy926, U937, and HL-60 cells under various exposure conditions. [The Working Group noted that the conclusions that could be drawn from this study were limited since the data analysis was carried out using a single RNA pool for each condition, making it impossible to estimate the true biological variance for statistical inference testing. Furthermore, no validation of results by RT-PCR was performed.]

Zeng *et al.* (2006) exposed human MCF7 breast-cancer cells to intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 2.0 or 3.5 W/kg) for 24 hours. No statistically significant differences were observed at the lower SAR, but five differentially expressed genes were detected in cells exposed at the SAR of 3.5 W/kg. [These findings were not validated with RT–PCR.]

Hirose *et al.* (2006) observed no noticeable changes in *TP53*-related gene expression in human A172 or IMR-90 cells exposed to RF radiation at 2142.5 MHz (SAR, 0.08–0.8 W/kg) for 24–48 hours. In this study the authors confirmed the absence of a response in the microarray analysis for four genes (*APAF1*, *TP53*, *TP53BP2* and *CASP9*) involved in *TP53*-mediated apoptosis by use of RT–PCR. In a similar study, Hirose *et al.* (2007) exposed the same two cell lines to RF radiation at 2142.5 MHz (SAR, 0.08–0.8 W/kg) for 2–28 hours. Despite assessing a variety of exposure conditions, including exposure duration, signal modulation and SAR levels, the authors reported no differential expression in hsp-related genes under any of the conditions tested in either cell line.

Qutob *et al.* (2006) exposed human glioblastoma-derived (U87MG) cells to pulsed-wave RF radiation at 1900 MHz (SAR, 0.1, 1 or 10 W/kg) for 4 hours. There was no evidence for differential gene expression in any of the exposed samples relative to the sham-exposed cells. As a positive control, exposure to heat-shock (43 °C, 1 hour) did induce several stress-responsive genes. In an extension of this study, the same research group exposed U87MG cells to RF radiation at 1900 MHz (SAR, 0.1, 1 or 10 W/kg) for 24 hours, and harvested RNA at 6 hours after exposure. In addition, the human-derived monocyte cell line (Mono-Mac-6) was exposed under similar conditions for 6 hours, and RNA was harvested either immediately or 18 hours after exposure. No evidence for differential gene expression was observed in either cell line, at any SAR or time-point tested (Chauhan *et al.*, 2007a).

Huang *et al.* (2008a) exposed human-derived Jurkat cells to RF radiation at 1763 MHz (SAR, 10 W/kg) for 1 hour per day, for 3 days. Genome-wide analysis did not identify any genes that were differentially expressed at a significant level ($P < 0.05$) with a greater than twofold change, but 10 genes were identified with a 1.3-fold change, with $P < 0.1$.

Sekijima *et al.* (2010) exposed three human cell lines (A172, glioblastoma; H4, neuroglioma; IMR-90 fibroblasts) to continuous-wave or W-CDMA-modulated RF radiation at 2142.5 MHz (SAR, 0.08, 0.25 or 0.8 W/kg) for up to 96 hours. Differential expression of a small number of genes was observed in each cell line. Ribosomal protein S2, growth arrest-specific

transcript 5, and integrin beta 5 were differentially expressed in H4 cells at the two higher SARs tested. [These findings were not validated with RT-PCR.]

Sakurai *et al.* (2011) assessed differential gene expression in a normal human astroglia cell-line (SVGp12) exposed to continuous-wave RF radiation 2450 MHz at (SAR, 1, 5 or 10 W/kg) for 1, 4, or 24 hours. With the high-throughput microarray, this study identified 17 genes that were upregulated and 11 that were downregulated in response to exposure to RF radiation. However, RT-PCR analysis found that the expression of these genes was not statistically different from that in the sham-exposed control group. [The Working Group noted that these results highlight the importance of proper validation of results generated by means of high-throughput screening.]

(iii) Transcriptomics studies in cultured mammalian cells

Whitehead *et al.* (2006) exposed C3H 10T½ mouse cells to RF radiation at 847.74 MHz (CDMA) or at 835.2 MHz (FDMA) (SAR, 5 W/kg) for 24 hours. Three independent experiments were conducted for each of the signal modulations, and matching samples were exposed to X-radiation (0.68 Gy) as positive controls. By intercomparison of the six sham-exposed samples an empirical estimate was made of the false-discovery rate. From the results of this analysis, the authors concluded that all of the gene-expression changes found after exposure to RF radiation were false positives, and that exposure to RF radiation had no effect on gene expression. No validation with RT-PCR was conducted. [The Working Group noted that genes responding to RF radiation were disregarded on the basis of the calculated false-discovery rate, rather than validated by means of RT–PCR. This was not scientifically justified as genes that were not false-positives may have been accidentally disregarded. Therefore, this study provided little useful information.]

Zhao *et al.* (2007a) investigated the expression of genes related to apoptosis in primary cultured neurons and astrocytes isolated from ICR mouse embryos aged 15 days. The cells were exposed to GSM-modulated RF radiation at 1900 MHz (SAR not given) from a mobile phone placed over the culture dish for 2 hours. Upregulation of several genes involved in the apoptotic pathway was observed, including *Casp2*, *Casp6* and *Pycard*. For the astrocytes, these effects were exposure-dependent, and not observed after sham-exposure (with the mobile phone on "stand-by"). These results were confirmed by RT-PCR analysis. [The Working Group noted that this study had some methodological deficiencies. The cells were exposed to RF radiation from a mobile phone under poorly defined experimental conditions with regards to control for electromagnetic-field components, such as SAR levels within the cell cultures during exposure.]

In a second study, Zhao *et al.* (2007b) observed significant changes in gene expression in primary rat neurons exposed to intermittent (5 minutes on, 10 minutes off) GSM-modulated RF radiation at 1800 MHz (SAR, 2 W/kg) for 24 hours. Ten downregulated and 24 upregulated genes were identified among the 1200 genes that were screened, with "fold-change" as the analysis criterion. These findings were confirmed by RT-PCR analysis of 17 of the upregulated and 8 of the downregulated genes, showing fair agreement with the microassay data.

Nylund *et al.* (2009) examined the proteome of human endothelial cells (EA.hy926) exposed to GSM-modulated RF radiation at 1800 MHz (SAR, 2 W/kg) for 1 hour. In 2D gel-electrophoresis, eight proteins were found to be differentially expressed in exposed cells, three of which were identified as SRM, GRP78, and PSA1. Western blotting did not confirm the response of GRP78 [SRM and PSA1 not tested due to lack of specific antibodies]. No effect was seen on the

expression of vimentin or HSP27 protein, which were found to respond to radiation at 900 MHz in earlier studies (see above). In a subsequent study, Nylund *et al.* (2010) exposed umbilical vein endothelial cells (HUVEC) and human brain microvascular endothelial cells (HBMEC) to the same type of RF radiation. No effects on protein expression were reported.

[Of the numerous studies that investigated the potential for RF radiation to modify gene-transcription and protein-expression levels in a variety of animal models *in vivo* and human models *in vitro*, some reported effects under conditions where the possibility of thermal confounding could not be excluded. Other studies reported alterations in gene/protein expression under non-thermal exposure conditions, but typically in single, usually unreplicated experiments, or under experimental conditions with methodological shortcomings. There were no studies in human populations. Overall, there was weak evidence that exposure to RF radiation affects gene and protein expression.]

4.4 Other relevant effects

4.4.1 Humans

(a) Neuroendocrine system

The majority of studies on the effects of exposure to RF radiation on the endocrine system in volunteers have focused on hormones released into the blood stream by the pineal and pituitary neuroendocrine glands. Both are situated in the brain and are intimately connected with and controlled by the nervous system. Some studies have investigated urinary excretion of the major melatonin metabolite: 6-sulfatoxymelatonin (aMT6s). Fewer studies have been carried out on circulating concentrations of pituitary hormones or hormones released from other endocrine glands, such as the adrenal cortex. The pituitary hormones exert a profound influence on body metabolism and physiology, particularly during development and reproduction, partly via their influence on the release of hormones from other endocrine glands situated elsewhere in the body. The main pituitary hormones investigated in studies on electromagenetic fields are thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), which regulates the function of the adrenal cortex and particularly the release of cortisol, and growth hormone (GH). Pituitary hormones with important sexual and reproductive functions have also been studied, particularly follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL). ACTH, cortisol and prolactin are also involved in the response to stress, and were often used as a marker for the effects of exposure to RF radiation.

No cumulative effects on serum melatonin or pituitary hormones were observed after repeated exposure to RF radiation for 1 month. Most studies did not report an effect after a single exposure, but the statistical power of these studies was often insufficient because of the small number of volunteers involved (Mann *et al.*, 1998; de Seze *et al.*, 1999; Radon *et al.*, 2001; Bortkiewicz *et al.*, 2002; Braune *et al.*, 2002; Jarupat *et al.*, 2003; Wood *et al.*, 2006).

(b) Neurobehavioural effects

(i) Electrical activity of the brain

The electroencephalogram (EEG) reflects synchronous activity in relatively large populations of cortical neurons. The "spontaneous" EEG of subjects who are awake is generally divided into several frequency bands, in which the relative amount of activity depends on the psychological state of the subject and the nature of the cognitive function in which she or he is engaged. The designation of the frequency bands is not always strictly applied, which results in specific frequencies sometimes being assigned to different bands in different studies. Generally, the following division is used: delta (δ) < 4 Hz; theta (θ) 4–8 Hz; alpha (α) 8–12 Hz; beta (β) 12–30 Hz;

and gamma (γ) > 30 Hz. Slightly different band designations are used by some authors, which are also cited in this Volume. The functional significance of these different components of the normal "waking" EEG is poorly understood. Thus, while a demonstration that mobile-phone signals influence these components would be indicative of a biological effect of such signals, interpretation of the effect would be uncertain. In addition, intra-individual variability is very high. In contrast, EEG patterns associated with sleep are well characterized and routinely used as indices of the different sleep stages that a typical healthy individual will experience during the night. Only studies on EEG during sleep are discussed here.

A review of studies on EEG during sleep and RF radiation was compiled by Hamblin & Wood (2002) and more recently, with a broader scope, by Kwon & Hämäläinen (2011). They cited studies by Mann & Röschke (1996), Mann *et al.* (1998), Wagner *et al.* (1998, 2000), Borbély *et al.* (1999), Huber *et al.* (2000, 2002, 2003), Loughran *et al.* (2005), Fritzer *et al.* (2007), Hung *et al.* (2007), Regel *et al.* (2007b), and Lowden *et al.* (2011). Some but not all studies on exposure to RF radiation during sleep have indicated increased EEG power in α or β bands. A reported shortening of sleep latency could not be reproduced. Other studies that looked at exposure to RF radiation for 30 minutes before going to sleep also showed variable results, sometimes reporting increases in α and β band power. In one study this was observed only after exposure to a modulated but not a continuous RF radiation signal, while in another study a dose-dependent increase in α and β power was seen. Two studies reported an increase in time taken to fall asleep. A recent study by Lowden *et al.* (2011) indicated that self-reported differences in sensitivity to emissions from mobile-phone use were not reflected in sleep parameters.

[The Working Group concluded that exposure to a GSM-type signal may result in minor effects on brain activity during sleep.]

(ii) Auditory and vestibular systems

As mobile phones are held close to the ear, various studies have checked for possible effects of exposure to mobile-phone type (GSM) RF radiation on the vestibular (balance) and cochlear (auditory) organs that comprise the inner ear. The hair-cell receptors present in each organ respond to head movement or to audible sound. This topic was recently reviewed by Kwon & Hämäläinen (2011), who concluded that neurophysiological studies showed no significant effects on cochlear and brainstem auditory processing, or on the vestibular system. [The Working Group noted that the results on spontaneous and evoked electrical activity in the brain were inconsistent.]

(iii) Cognitive performance

Studies on cognitive performance in relation to exposure to RF radiation have been carried out in healthy adult volunteers, in adults who self-reported a variety of symptoms such as headaches in the vicinity of RF sources, and in children and adolescents, following the recommendations of IEGMP (2000).

Dynamic changes in brain anatomy occur throughout childhood and adolescence. The amount of white matter, which corresponds to myelination of nerve axons and is related to the speed of neuronal processing, increases linearly throughout adolescence. Changes in the amount of grey matter are thought to reflect changes in size and complexity in neurons, such as the number of synaptic connections, rather than changes in number of neurons themselves. These changes are considered to be related to maturation of behaviour; they are more complex and continue into the early 20s (Giedd, 2004).

Reviews of studies on neurobehavioural effects of exposure to RF radiation have been compiled by Barth *et al.* (2008) and more recently

by Kwon & Hämäläinen (2011). The latter authors indicated that improvement of cognitive performance after exposure to RF radiation, as reported in earlier studies, had not been confirmed in more recent behavioural studies with improved analyses.

(iv) Subjective symptoms

Some people self-report having a variety of subjective complaints, including headaches and migraines, fatigue, skin itches, and sensations of heat, after exposure to RF radiation (Frey, 1998; Hocking, 1998; Chia *et al.*, 2000; Hocking & Westerman, 2000; Sandström *et al.*, 2001; Santini *et al.*, 2002a, b). These symptoms are attributed to exposures at home or at work to RF radiation emitted by mobile phones, nearby base stations, digital enhanced cordless telecommunications (DECT) cordless phones and, more recently, wireless local area network (LAN) systems. Less commonly reported symptoms include dizziness, blurred vision, memory loss, confusion and vagueness, toothaches, and nausea. An increasing number of these people consider themselves to be electrosensitive. Provocation studies provide the most direct way of studying a possible effect of exposure to RF radiation on the occurrence of such symptoms. A weakness of these studies is that they focus on direct, short-term interactions, while symptoms may only occur after a longer exposure. In their review, Kwon & Hämäläinen (2011) conclude that provocation studies provided no evidence that the subjective symptoms could be attributed to mobile-phone use, which suggests that there are other explanations for the induction of such symptoms in hypersensitive people.

(c) Thermal effects and thermoregulation

There is an established literature on cardiovascular responses to heating associated with exposure to RF radiation, such as those involved in thermoregulation. Several studies addressed these end-points in connection with thermoregulation and heat-stress disorders, to place the possible health consequences of such heating into a broader occupational and environmental context (ICNIRP, 2009).

RF energy is absorbed by the body, resulting in the production of heat due to an increase in molecular rotational and translational kinetic energy. The absorbed heat energy is distributed throughout the body in the circulation and is partially lost to the external environment. Significant whole-body heating has a major impact on cardiovascular physiology. In addition, the ability to carry out cognitive tasks is compromised before physiological limits of tolerance are reached (Hancock & Vasmatzidis, 2003). ICNIRP (2009) has indicated that adequately hydrated, inactive, healthy volunteers exposed to RF radiation under laboratory conditions will accommodate whole-body heat loads of approximately 1 W/kg for 45 minutes at environmental temperatures of up to 31 °C, to 6 W/kg for at least 15 minutes at ambient temperatures, with increased skin blood-flow and profuse local sweating, but with minimal changes in core temperature. With regard to local heating of the skin, skin blood-flow and local sweating increase with increasing skin temperature by up to 4 °C in response to a local peak SAR of about 15 W/kg at the irradiated site, but it is not known how less superficial and less vascular tissues may respond.

A full assessment of whole-body heat stress can only be properly derived from a consideration of all sources of heat and from the ease with which heat can be lost from the body, as given by the heat-balance equation. Heat gain through solar radiation or other sources of radiant heat may also have to be taken into account. The main adverse health effects expected to result from excessive heat loads are heat-related disorders such as heat exhaustion and, in elderly people, an increase in the risk of heat-related mortality (Lakatta, 2002). These effects are well documented in people exposed to hot environments and in elderly people during prolonged periods

of hot weather, but have not been associated with exposure to RF radiation. In addition, adverse effects on cognitive function may be expected to result from increased body temperature, with the potential to increase accident rates, but this has proven to be difficult to quantify in studies with volunteers. Several studies of acute exposure have been carried out to assess the adverse effects of increased tissue temperature in experimental animals, often in the context of providing guidance on the use of ultrasound or hyperthermia treatments in clinical practice (Ryan *et al.*, 1997). Lesions, including those that result from cell death, generally occur when temperatures exceed 42 °C for more than about 1 hour. The central nervous system and testes appear to be particularly susceptible to heat-induced damage and show significant changes in cell numbers after exposures to 40–41 °C and higher.

Studies on mobile-phone use by volunteers have investigated the effects of RF radiation from mobile phones at levels generally assumed to be too low to induce significant heating. In principle, such "athermal" effects on the cardiovascular centres of the brainstem, which regulate the heart and circulation via outflow in the sympathetic and parasympathetic systems, are possible (Benham *et al.*, 2003; Patapoutian *et al.*, 2003; Moran *et al.*, 2004; Glaser, 2005; Bandell *et al.*, 2007; Foster & Glaser, 2007). Several studies focused on possible effects on heart rate, heart-rate variability, blood pressure and cerebral blood flow. There is no clear evidence of an effect of such exposure on resting heart rate or blood pressure. However, small but inconsistent variations in heart-rate variability have been reported.

(d) Cerebral blood flow and neural biochemical activity

Changes in regional cerebral blood flow could reflect (or cause) local changes in neural activity. There are some indications of changes in regional cerebral blood flow during and after exposure to RF radiation. In their review, Kwon & Hämäläinen (2011) concluded that approaches such as measurement of the haemodynamic response in the brain were promising, but the findings were few and not conclusive. The studies reviewed were Braune *et al.* (1998, 2002), Reid & Gettinby (1998), Borbély *et al.* (1999), Huber *et al.* (2000, 2002, 2003, 2005), Haarala *et al.* (2003a), Sandström *et al.* (2003), Tahvanainen *et al.* (2004), Aalto *et al.* (2006), Nam *et al.* (2006), Barker *et al.* (2007), and Parazzini *et al.* (2007). Also linked to cerebral blood flow, a more recent study by Volkow *et al.* (2011) using glucose-uptake positron-emission tomography (PET) showed an increase in local cerebral metabolism after exposure to a mobile phone in reception mode.

[The small changes seen in electrical activity in the brain and possibly in regional cerebral blood flow may not have functional significance. No consistent effects on cognitive performance have been found, although the use of a large variety of techniques to assess cognitive performance makes it difficult to directly compare the results of different studies. No research data were available that would link these findings to cancer.]

4.4.2 Experimental systems: in vivo

(a) Oxidative stress

Numerous experiments have been conducted to explore the possibility that exposure to RF radiation may trigger oxidative stress in tissues of exposed animals (most frequently rats). Markers of oxidative stress include increased levels of malondialdehyde (indicative of lipid peroxidation), nitric oxide (NO), and reduced glutathione (GSH), and the activities of antioxidant enzymes such as SOD, catalase, or GSH-Px, or of pro-oxidant enzymes such as xanthine oxidase (XO).

(i) Brain

[Many of the studies in this section used a mobile phone as the source of exposure to RF radiation, which limits the value of these studies in hazard identification.]

Irmak *et al.* (2002) exposed male rabbits to radiation from a commercially available GSM mobile phone (900 MHz; peak power, 2 W; average power density, 0.02 mW/cm^2) for 30 minutes per day, for 7 days. The telephones were positioned "in close contact with the rabbits." The concentrations of malondialdehyde and NO, and activities of several relevant enzymes were measured in brain and serum of exposed and sham-exposed rabbits. No significant changes were noted in any parameter in the brain; a significant increase in SOD activity (P = 0.042) and a significant decrease in concentrations of NO (P = 0.004) were observed in the serum of exposed rabbits.

Ilhan *et al.* (2004) exposed female rats to a GSM signal from a mobile phone (900 MHz; continuous wave; analogue phone), 1 hour per day, for 7 days, at SARs of 2 W/kg (brain) or 0.25 W/kg (whole body), with or without administration of a *Ginkgo biloba* extract. Treatment with this extract by daily oral gavage started 2 days before and was continued throughout the 7 days of exposure to RF radiation. Immediately after exposure, histopathological changes and biochemical markers of oxidative stress were evaluated in the brain. "Dark" neurons (degenerative neurons that can be visualized by staining with cresyl violet) were detected in all locations, particularly in the cortex, hippocampus and basal ganglia. The concentrations of NO and malondialdehyde, and the activities of the enzymes XO and adenosine deaminase were increased in brain tissues, while the activities of SOD and glutathione peroxidase were decreased. Co-exposure with the *Ginkgo biloba* extract prevented these effects. [The Working Group noted that the experimental protocol in this study was imprecise. The SAR was given without any information on how it was derived; the mention of analogue with GSM was contradictory.]

Elhag *et al.* (2007) exposed rats of unspecified strain and sex to RF radiation from a GSM mobile phone (900 MHz) for either 1 hour, or for 15 minutes per day, for 4 days, at a SAR of 0.25 W/kg, and reported a reduction in concentrations of vitamins C and A in serum, a decreased level of vitamin E in erythrocytes, and a reduction in the activities of catalase and SOD and concentrations of reduced glutathione in erythrocytes. [The Working Group noted the imprecise experimental protocol of this study, and did not take the results into further consideration.]

Meral *et al.* (2007) exposed guinea-pigs to RF radiation at 890–915 MHz (SAR, 0.95 W/kg) from a mobile phone for 12 hours per day (11 hours 45 minutes "stand-by" and 15 minutes "on") for 30 days. At the end of the exposure period, lipid peroxidation, enzymatic activities and vitamins in blood and brain tissue were measured biochemically, and compared between exposed and non-treated controls. Increased concentrations of malondialdehyde, and reduced glutathione concentrations and catalase enzyme activity were observed in brain tissue, but there was no change in levels of vitamins A, E and D3 in the brain. In the blood of the exposed animals, increased concentrations of malondialdehyde, vitamins A, D3 and E, and catalase enzyme activity were seen, as well as decreased levels of glutathione. [The Working Group noted the lack of sham-exposed controls.]

Ammari *et al.* (2008) studied the activity of cytochrome oxidase in the brain of rats exposed to RF radiation at 900 MHz (GSM) from an RF generator, for 15 minutes per day for 7 days at a SAR (brain) of 6 W/kg, or for 45 minutes per day for 7 days at a SAR of 1.5 W/kg. While exposure at the lower SAR had no effect, exposure at a SAR of 6 W/kg induced a decrease in the activity of cytochrome oxidase in some areas of the rat brain (frontal cortex, posterior

cortex, hippocampus and septum). [This result showed that GSM signals at high SAR may affect the activity of cytochrome oxidase in the brain, which is a metabolic marker of neuronal activity.]

Sokolovic *et al.* (2008) exposed male rats to continuous-wave RF radiation at 900 MHz (GSM) from a mobile phone placed in the cage, for 4 hours per day during the light period (06:00–18:00) for 20, 40 or 60 days, at an estimated whole-body SAR of 0.043–0.135 W/kg, with or without daily intraperitoneal injections of melatonin (2 mg/kg bw) or saline. A false phone was placed in the cages of the control groups and the groups receiving melatonin only. A significant 20–50% increase in brain concentrations of malondialdehyde and carbonyl groups was observed during exposure. Catalase activity was decreased (–20%) during exposure, while the activity of XO was increased (15–25%) after 40 and 60 days of exposure. Treatment with melatonin prevented increases in malondialdehyde content and XO activity in brain tissue after 40 and 60 days of exposure.

Dasdag *et al.* (2009) exposed male Wistar rats to RF radiation at 900 MHz (GSM) delivered to the head for 2 hours per day, 7 days per week, for 10 months. No difference was found in oxidative-stress indexes between the groups, while total oxidant capacities and catalase in the brain were significantly higher ($P < 0.05$) in the exposed group than in the sham-exposed group.

Imge *et al.* (2010) exposed female rats to RF radiation at 900 MHz (GSM) from a mobile phone (SAR, 0.95 W/kg) placed 10 cm above the cages, for 4 × 10 minutes per day, for 4 weeks, with or without daily oral administration of vitamin C (250 mg/kg bw). The activities in brain tissue of 5′-nucleotidase and catalase were significantly reduced compared with those of the non-treated control group, and there was a non-significant reduction in the activity of glutathione peroxidase and in concentrations of malondialdehyde in the brain. Vitamin C had a protective effect in some of these analyses. [The Working Group noted the lack of sham-exposed controls.]

(ii) Kidney

The justification for studying oxidative stress in the kidney following exposure to electromagnetic fields stems from the fact that the kidney would be the organ with the greatest exposure when a mobile phone is worn at the belt.

Oktem *et al.* (2005) exposed groups of eight Wistar albino rats to RF radiation at 900 MHz (GSM; average power density, 1.04 mW/cm^2) for 30 minutes per day for 10 days, with or without treatment with melatonin (100 µg/kg bw; subcutaneous injection) before the daily exposure to RF radiation. SAR values were not reported. Increases in tissue concentrations of malondialdehyde and urinary *N*-acetyl-β-D-glucosaminidase (NAG), a marker of renal tubular damage, were observed. The activities of SOD, catalase, and GSH-Px were reduced. Administration of melatonin reversed or prevented these effects.

The same group (Ozguner at al., 2005b) compared the protective effects of melatonin (100 µg/kg bw; subcutaneous injection) and of caffeic acid phenethyl ester (CAPE; dose unclear), a component of honey-bee propolis used in traditional medicine, in Sprague-Dawley rats exposed to RF radiation. The experimental protocol was similar to that of Oktem *et al.* (2005), with antioxidants being injected daily for 10 days before exposure to RF radiation at 900 MHz (GSM; average power density, 1.04 mW/cm^2). Urinary NAG and renal MDA were increased, while renal SOD and GSH-Px were decreased. Melatonin and CAPE reversed or prevented many of these effects, with melatonin being the more potent antioxidant. The results were similar to those reported previously, with the exception of catalase, the activity of which was not modified.

(iii) Myocardium

Ozguner *et al.* (2005a) assessed the protective effects of CAPE in myocardium of Sprague-Dawley rats exposed to RF radiation at 900 MHz, using an experimental protocol similar to that used for studies in the kidney (see above) and found comparable results.

(iv) Eye

Ozguner at al. (2006) compared the protective effects of melatonin and CAPE (a component of honey-bee propolis used in traditional medicine) on oxidative stress induced in rat retina by exposure to RF radiation at 900 MHz (whole-body SAR, 0.016 W/kg; local SAR at the head, 4 W/kg). The experimental protocol was similar to that in Ozguner *et al.* (2005b): antioxidants were injected daily for 60 days (rather than 10 days) before exposure to RF radiation for 30 minutes per day for 60 days (rather than 10 days). Significantly increased ($P < 0.0001$) retinal concentrations of NO and MDA were found in exposed rats, which remained at control values after pre-treatment with melatonin and CAPE. Likewise, the activities of SOD, GSH-P*x* and CAT were significantly reduced in the retina of exposed rats. Again, prior treatment with melatonin and CAPE prevented this reduction in the activities of these antioxidant enzymes. These data indicated that antioxidants reduce oxidative stress in the rat retina caused by long-term exposure to RF radiation. [The Working Group was uncertain about the dosimetry in this study, and noted the lack of a cage-control group to assess the effect on the rats of being restrained in a tube during the exposures.]

Balci *et al.* (2007) exposed female rats to RF radiation at 900 MHz from a mobile phone (GSM; SAR, 1.2 W/kg), placed 10 cm above the cages, for 4 × 10 minutes per day, for 4 weeks, with or without daily oral administration of vitamin C (250 mg/kg bw). In the cornea, a significant increase was found in the concentration of malondialdehyde and in the activity of catalase compared with the control group and with the exposed group receiving vitamin C, while the activity of SOD was decreased. In the lens tissues, the malondialdehyde concentration was significantly increased, but no significant differences in the activities of SOD, GSH-Px or catalase were observed. The presence of vitamin C generally diminished the effects of exposure to RF radiation. [The Working Group noted several design flaws in this study (e.g. the exposure system, the absence of dosimetry, absence of sham-exposed controls) and did not further consider these results.]

(v) Liver

Ozgur *et al.* (2010) investigated oxidative damage and antioxidant-enzyme status in the liver of guinea-pigs exposed to RF radiation at 1800 MHz (GSM; SAR, 0.38 W/kg) for 10 or 20 minutes per day, for 7 days. In this study the potential protective effects of *N*-acetylcysteine (NAC) and epigallocatechin-gallate (EGCG) were also investigated. A significant increase in the concentrations of malondialdehyde and nitrogen oxides (NO_x) and a reduction in the activities of SOD, myeloperoxidase and GSH-Px were observed in the liver of exposed guinea-pigs. Some of these changes appeared to be proportional to the duration of exposure). In addition, treatment with NAC induced an increase in hepatic GSH-Px activities, whereas treatment with EGCG attenuated concentrations of malondialdehyde.

Tomruk *et al.* (2010) evaluated the effects of whole-body exposure to RF radiation at 1800 MHz (GSM) for 15 minutes per day, for 1 week, on oxidative DNA damage and lipid peroxidation in the liver of nonpregnant or pregnant New Zealand White rabbits, and in their newborns. Concentrations of malondialdehyde increased significantly in exposed nonpregnant and pregnant animals compared with nonpregnant controls, but there was no difference between exposed and sham-exposed pregnant rabbits. The same results were observed with lipid

peroxidation, measured by means of the ferrous oxidation-xylenol orange [FOX] assay. Exposure to RF radiation had no effect on the amount of oxidative DNA damage (8-OHdG adducts) in the liver of RF-exposed and sham-exposed nonpregnant and pregnant rabbits. No differences in concentrations of malondialdehyde and 8-OHdG were found in the liver of newborns exposed to RF radiation *in utero* compared with newborns of sham-exposed mothers. However, a significant reduction in lipid peroxidation, *i.e.* reduced FOX levels, in the liver of RF-exposed newborns was observed. [The Working Group noted that SAR values were not stated.]

(vi) Miscellaneous

Mailankot *et al.* (2009) exposed adult male Wistar albino rats to RF radiation at 900/1800 MHz (SAR not given) from a GSM mobile phone "in active mode" for 1 hour per day for 28 days, while control rats were exposed to a mobile phone "without battery." There was no difference in sperm counts in the epididymis between exposed and control rats, but a 40% reduction in the proportion of motile sperm was observed after exposure. In addition, the concentration of malondialdehyde was significantly increased and intracellular GSH was significantly reduced in the testis and epididymis of exposed rats, compared with sham-exposed controls, together with a significant decrease in intracellular GSH in both testis and the epididymis of RF-exposed rats.

Kumar *et al.* (2010) exposed male Wistar rats to continuous RF radiation at 10 or 50 GHz (SAR, 0.014 and 0.0008 W/kg, respectively) for 2 hours per day, for 45 days. Total levels of ROS and catalase activity were higher and the proliferative index, and the activities of SOD and reduced GSH-Px in the serum were lower in exposed rats than in sham-exposed controls.

(b) Differentiation and apoptosis

Dasdag *et al.* (2003) exposed male Sprague-Dawley rats to RF radiation at 900 MHz from commercially available mobile phones (average calculated whole-body SAR, 0.52 W/kg; peak SAR, 3.13 W/kg) for 20 minutes per day, 7 days per week, for 1 month. The mobile phones were placed 0.5 cm under the cages. There were no differences between exposed and sham-exposed groups in terms of structure of testes, sperm counts, phospholipid composition or Tp53 immunoreactivity. [The Working Group noted the ill-defined exposure set-up and the approximative SAR calculations.]

In a study mentioned before, Dasdag *et al.* (2009) exposed male Wistar rats to RF radiation at 900 MHz (GSM; SAR, 0.19–0.58 W/kg) delivered to the head for 2 hours per day, 7 days per week, for 10 months. The apoptosis score – based on immunostaining of active caspase-3 – in the brain of the exposed rats was significantly lower than in sham-exposed or cage-control rats.

Apoptosis induced in the endometrium was studied by Oral *et al.* (2006) by exposing female Wistar albino rats in a plastic tube to RF radiation at 900 MHz (GSM) (SAR, 0.016–4 W/kg) for 30 minutes per day, for 30 days. Different group of rats received vitamin E (50 mg/kg bw) or vitamin C (20 mg/kg bw) by intramuscular or intraperitoneal injection, respectively, just before the daily exposure to RF radiation. Increased concentrations of malondialdehyde (indicative of lipid peroxidation) and enhanced apoptosis were observed in endometrial tissue (stromal cells) of exposed rats. These effects were partly reverted by vitamin treatment. Using the same experimental protocol, Guney *et al.* (2007) observed an increase in oxidation products (NO, malondialdehyde), a decrease in activities of antioxidant enzymes (SOD, catalase, GSH-Px), and diffuse and severe apoptosis in the endometrial surface epithelial and glandular cells and in

stromal cells. [Both studies lacked details on SAR measurement.]

Odaci *et al.* (2008) examined paraffin-embedded sections of the brain of rats aged 4 weeks born from females exposed to RF radiation at 900 MHz (GSM; calculated whole-body SAR, 2 W/kg), for 60 minutes per day during the entire gestation period. A slight but statistically significant reduction in the number of granule cells in the dentate gyrus of pups of exposed dams was observed; this reduction may affect postnatal behavioural and cognitive functions. [The Working Group noted the apparent lack of a sham-exposed control group.]

More recently, Sonmez *et al.* (2010) examined paraffin-embedded sections of the cerebellum of female rats aged 16 weeks exposed to RF radiation at 900 MHz (calculated average SAR, 0.016 and 2 W/kg, respectively, for whole-body or head-only) for 1 hour per day, for 28 days. A significant reduction in the number of Purkinje cells was observed in the cerebellum of exposed rats compared with sham-exposed controls and cage controls.

[The Working Group concluded that there was weak evidence that exposure to RF radiation at 900 MHz induces differentiation or apoptosis in the brain or endometrium of exposed rats.]

(c) Blood–brain barrier

The blood–brain barrier regulates exchange between blood and the brain. An increase in the normally low permeability of this barrier for hydrophilic and charged molecules after exposure to RF radiation could potentially be detrimental by enabling the extravasation of substances that could potentially act as brain carcinogens.

In vivo, several methods have been used to evaluate the integrity of the blood–brain barrier. These methods are based either on assessment of the permeability of the barrier to endogenous molecules such as albumin, which can be visualized by immunohistochemistry on brain sections, or on the injection of dyes (Evans blue) or labelled molecules that do not cross the blood–brain barrier under normal physiological conditions and hence may serve as permeability markers. Models of brain injury (e.g. cold injury or chemical injury) are informative positive controls in these experiments. Another method comprises the evaluation of alterations in nervous tissue by detecting degenerating neurons ("dark neurons") through staining with cresyl violet, or with the fluorescent molecule Fluoro-Jade B, which is more specific for neurons.

Dozens of experiments in rodents have assessed the functioning of the blood–brain barrier in animals exposed to various intensities of RF radiation at frequencies ≥ 900 MHz (for reviews, see Stam, 2010 and Nittby *et al.*, 2011). Here are described only experimental studies of exposure at frequencies ≥ 900 MHz and at exposure levels that did not – or were unlikely to – produce a thermal effect: in the rat brain, hyperthermia of > 1 °C induces alterations in the blood–brain barrier. It should be noted also that anaesthesia itself may modify the permeability of the blood–brain barrier.

One research group has reported effects on the permeability of the blood–brain barrier and alterations in nervous tissue (dark neurons) after exposure of Fisher 344 rats (males and females) to continuous or GSM-modulated RF radiation at 900 and 915 MHz, with SARs of 2–5 W/kg. Among recently published studies from this group, three (Eberhardt *et al.*, 2008; Nittby *et al.*, 2009, 2011) reported an increase in permeability to albumin at 1 or 2 weeks after 2 hours of exposure to a 900 MHz GSM signal (SAR, 0.0001–0.13 W/kg). Another study from this group (Grafström *et al.*, 2008) assessed permeability of the blood–brain barrier 5–7 weeks after exposure to a GSM signal (SAR, 0.0006–0.6 W/kg) for 2 hours per week for 55 weeks, and found no increase in permeability using several markers, and no appearance of dark neurons.

Masuda *et al.* (2009) did not observe albumin extravasation or appearance of dark neurons

in experiments in two-compartment transverse electromagnetic (TEM) transmission line cells. Male Fischer F344 rats were exposed to a 915 MHz GSM signal (whole-body SAR, 0.02, 0.2 or 2 W/kg) for 2 hours. Positive controls (cold and chemical injury) were included. Analyses were performed 14 and 50 days after exposure.

McQuade *et al.* (2009) did not observe any leakage of albumin across the blood–brain barrier in male Fischer 344 rats sham-exposed or exposed to 915 MHz RF radiation (SAR, 0.0018–20 W/kg) for 30 minutes in TEM cells. Both continuous-wave and pulsed modes of 16 and 217 Hz were used, with pulse parameters based on those in studies from the research group mentioned above (Persson *et al.*, 1997). Positive controls (hyperthermia at 43 °C, and urea 10 M) were included. Albumin extravasation was investigated by immunohistochemical staining of brain sections. A subset of the microscopic slides was sent to Sweden and analysed by scientists associated with the original studies. No alterations in the blood–brain barrier were observed at any exposure level.

De Gannes *et al.* (2009) found no changes in the integrity of the blood–brain barrier or neuronal degeneration in Fischer 344 rats exposed head-only to a 900 MHz GSM signal (brain-averaged SAR, 0.14 or 2 W/kg) for 2 hours. Complete numerical and experimental dosimetry was included in this study. Albumin leakage, dark neurons, or changes in neuronal apoptosis were not observed. [It is worthy of note that in these three studies, homogeneous samples of male rats of the same age and weight were used. The SAR values tested were higher or of a wider power range than in experiments of the Swedish group.]

[The Working Group concluded that despite consistent results from one laboratory, the experimental evidence did not support the notion that non-thermal RF radiation affects the permeability of the blood–brain barrier.]

4.4.3 Experimental systems: in vitro

(a) Human cells

(i) Free radicals and ROS

Free radicals are highly reactive molecules that carry unpaired electrons in the outer orbit. Free radicals that are derived from oxygen metabolism are known as reactive oxygen species (ROS). These radicals are continuously neutralized by antioxidants present in body tissues. When production of these species exceeds the scavenging capacity of antioxidants, oxidative stress results. Production of radicals is a known pathway involved in the development of cancer.

Lantow *et al.* (2006a, c) measured production of ROS and expression of HSPs (described in section 4.3.2.c (i)) in human Mono Mac 6 and K562 cells exposed to RF radiation at 1800 MHz (SAR, 0.5, 1.0, 1.5 or 2.0 W/kg) as three different GSM modulation signals, for 45 minutes. Heat and phorbol 12-myristate-13-acetate (PMA) induced a significant increase in superoxide radical anions and in the production of ROS. In general, no effects were observed from exposure to RF radiation alone or in combination with PMA or lipopolysaccharide. Lantow *et al.* (2006b) used human umbilical cord blood-derived monocytes and lymphocytes to examine release of ROS after continuous or intermittent (5 minutes on, 5 minutes off) exposure at 1800 MHz (SAR, 2 W/kg) for 30 or 45 minutes. Exposure to RF radiation did not enhance the effects of PMA. In another study from the same group, Simkó *et al.* (2006) exposed human Mono Mac 6 cells to RF radiation under similar conditions, but combined exposures were carried out with ultrafine particles. Exposure to RF radiation alone had no effect on radical production. In addition, RF radiation did not enhance the production of superoxide anion radicals induced by ultrafine particles.

Luukkonen at al. (2009) investigated intracellular production of ROS and DNA-damage induction in human SH SY5Y neuroblastoma

cells exposed to continuous-wave or pulsed-wave RF radiation at 872 MHz (SAR, 5 W/kg) for 1 hour. The experiments also involved combined exposure to RF radiation and menadione. The production of ROS was measured by use of the fluorescent probe dichlorofluorescein. No effects were seen from exposure to RF radiation alone. Consistent with the increase in DNA damage (described in Section 4.1.3.b.ii), the level of ROS measured after treatment with menadione was higher in cells exposed to a continuous-wave RF field. However, no effects of the pulsed-wave RF radiation were seen at identical SARs. In a second study using identical exposure conditions and the same cell line, Luukkonen *et al.* (2010) found no effects on ROS production induced by ferrous choride from continuous-wave or pulsed-wave RF radiation. This finding was consistent with lack of effect on DNA-damage induction in the same study, as described earlier.

Höytö *et al.* (2008a) exposed human SH-SY5Y neuroblastoma cells and mouse L929 fibroblasts to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg) for 1 hour or 24 hours, under isothermal conditions. To investigate possible combined effects with other agents, menadione was used to induce ROS, and *tert*-butylhydroperoxide (*t*-BOOH) was used to induce lipid peroxidation. After the 1-hour exposure, there was a statistically significant enhancement by RF radiation of *t*-BOOH-induced lipid peroxidation in SH-SY5Y cells exposed to the GSM-modulated signal. After the 24-hour exposure, there was a statistically significant increase by RF radiation of menadione-induced caspase-3-like protease activity in mouse L929 fibroblasts exposed to the GSM-modulated signal. No effects were seen in any of the other experimental conditions, or from exposure to RF radiation alone.

Purified human spermatozoa were exposed to RF radiation at 1800 MHz (SAR, 0.4 W/kg to 27.5 W/kg) (De Iuliis *et al.*, 2009). With increasing SAR, motility and vitality of the sperm cells were significantly reduced after exposure, while the mitochondrial generation of ROS and DNA fragmentation were significantly elevated. Furthermore, highly statistically significant relationships between SAR, the oxidative DNA damage biomarker 8-OHdG, and DNA fragmentation were observed in exposed cells. The temperature during these experiments was kept at 21 °C; the highest observed exposure-induced temperature increase was +0.4 °C, at SAR 27.5 W/kg; control experiments in which spermatozoa were incubated at 21 °C–50 °C – without RF radiation – indicated that the end-points measured were only significant above 40 °C.

Human sperm was exposed *in vitro* for 1 hour to RF radiation at 850 MHz (SAR, 1.46 W/kg) from a mobile phone in talk mode, and markers of oxidative stress were evaluated (Agarwal *et al.*, 2009). The results showed a significant increase in production of ROS in exposed samples and a decrease in sperm motility, viability, and in the ROS-total antioxidative capacity (ROS-TAC) score in exposed samples.

[The Working Group concluded that there was weak evidence that RF radiation activates a stress response or production of ROS in human cells under non-thermal conditions.]

(ii) Cell proliferation

Kwee & Raskmark (1998) exposed human AMA epithelial amnion cells to RF radiation at 960 MHz (GSM; SAR, 0.021, 0.21 or 2.1 mW/kg) for 20, 30, and 40 minutes at 37 °C. Cellular proliferation was assessed by means of the formazan test, and found to decrease linearly with exposure time at the lowest and highest SAR level. In a follow-up study, Velizarov *et al.* (1999) exposed human AMA cells to RF radiation at 960 MHz (GSM; SAR, 2.1 mW/kg) for 30 minutes at two different temperatures (39 °C and 35 °C), to evaluate whether the earlier results (see above) were temperature-dependent. There was a marginally significant reduction in cellular proliferation rate – measured with the formazan test – after the 30-minute exposure at both

temperatures (P = 0.086 and 0.072, respectively, based on 11 independent exeriments); the change in proliferation rate of the sham-exposed cells was not different at the two temperatures tested. The authors considered it unlikely that the effect of exposure to RF radiation on cell proliferation was a thermal effect.

Pacini *et al.* (2002) exposed human Detroit 550 skin fibroblasts to RF radiation at 960 MHz (GSM; estimated SAR, 0.6 W/kg) for 60 minutes. The radiation source was a mobile phone placed underneath the culture dish. No changes in the rate of cell replication were seen, as tested by [^{3}H] thymidine incorporation. [The use of a mobile phone as a radiation source made this study difficult to interpret; with only three replicates, the sample size was small.]

Capri *et al.* (2004a) exposed peripheral blood mononucleated cells from healthy volunteers to RF radiation at 900 MHz (GSM or continuous-wave; average SAR, 70–76 mW/kg) for 1 hour per day, for 2 or 3 days. Cells were treated with the mitogens PHA or alphaCD3 to stimulate replication. A statistically significant (P = 0.04) decrease in cell replication – as judged by [^{3}H] thymidine incorporation – was seen only for the cells exposed to the GSM RF-radiation and stimulated with the lowest dose of PHA; all other differences were non-significant. There was no effect at all after exposure to the continuous-wave RF radiation.

Marinelli *et al.* (2004) exposed human CCRF-CEM T-lymphoblastic leukaemia cells to continuous-wave RF radiation at 900 MHz (SAR, 3.5 mW/kg) for 2, 4, 12, 24, or 48 hours. There was a significant decrease in total viable cell number after 24 and 48 hours of exposure, and a significant increase in the percentage of apoptotic cells – measured by fluorescence-activated cell sorting (FACS) analysis – after 2 hours, which gradually diminished but remained significant after 24 and 48 hours of exposure. In addition, after 48 hours the number of cells that had started S-phase had increased, while the percentage of cells in growth-arrest diminished. These data support the notion that RF radiation may lead cancer cells to acquire an advantage to survive and proliferate. [The Working Group had some difficulty in understanding the discription of the exposure conditions in this study.]

Sanchez *et al.* (2006b) exposed reconstructed human primary keratinocytes to RF radiation at 900 MHz (GSM; SAR, 2 W/kg) for 48 hours. No apoptosis was induced in these cells, and there was no alteration of cell proliferation. A small increase in expression of heat-shock protein (Hsp) 70 was noted after 3 and 5 weeks of culture. Merola *et al.* (2006) exposed human LAN-5 neuroblastoma cells to RF radiation at 900 MHz (GSM; SAR, 1 W/kg) for 24, 48 or 72 hours, and found no effects on cellular replication. Gurisik *et al.* (2006) exposed human SK-N-SH neuroblastoma cells and monocytic U937 cells to 900 MHz (GSM-modulated) RF radiation (SAR of 0.2 W/kg) for 2 hours. There were no effects on cell-cycle distribution, apoptosis, or HSP levels. Lantow *et al.* (2006c) exposed human macrophagic Mono Mac 6 cells to pulse-modulated RF radiation at 1800 MHz (GSM-DTX; SAR, 2 W/kg) for 12 hours. No changes in cell-cycle distribution or cell proliferation were reported. Takashima *et al.* (2006) exposed human MO54 glioma cells to 2450 MHz continuous-wave RF radiation (SAR, 0.05, 0.5, 5, 50, 100, 200 W/kg) for 2 hours, or to intermittent RF radiation at 2450 MHz (mean SAR, 50 or 100 W/kg) for 2 hours. Exposure to continuous-wave RF radiation at 200 W/kg caused a decrease in cell replication and cell survival. Other exposures had no effect. [It should be noted that the temperature of the medium increased to 44.1 °C at exposures with SAR of 200 W/kg).] Sun *et al.* (2006) exposed human lens epithelial cells to GSM-modulated RF radiation at 1800 MHz (SAR, 1, 2, 3, 4 W/kg) for 2 hours. No effects of RF exposure were observed on cell proliferation (incorporation of bromodeoxyuridine) up to 4 days after exposure. Chauhan *et al.* (2007b) exposed human lymphoblastoid TK6,

lymphoblastic HL60 and myeloid Mono Mac 6 cells to intermittent (5 minutes on, 10 minutes off) pulse-modulated RF radiation at 1900 MHz (SAR, 1 and 10 W/kg) for 6 hours. There were no effects on cell-cycle progression.

[The Working Group concluded that there was weak evidence that exposure to RF radiation affects cell proliferation.]

(iii) Apoptosis

Defects in apoptosis-signalling pathways are common in cancer cells; apoptosis is an important mechanism by which damaged cells are removed, thus preventing the proliferation of potential cancer cells.

Marinelli *et al.* (2004) reported increased apoptosis, determined by flow cytometry and DNA-ladder analysis, in human CCRF-CEM T-lymphoblastoid leukaemia cells exposed to continuous-wave RF radiation at 900 MHz (SAR, 0.0035 W/kg) for 2–48 hours. Measurement of gene expression indicated activation of both TP53-dependent and -independent apoptotic pathways after shorter exposures (2–12 hours), while decreased pro-apoptotic signals were seen at longer exposure times (24–48 hours). As indicated above, these data support the notion that RF radiation may lead cancer cells to acquire an advantage to survive and proliferate. [The Working Group noted that the statistical comparisons with respect to FACS analysis were with unexposed, not sham-exposed cells.]

Port *et al.* (2003) exposed human myeloid leukaemia cells (HL-60) to pulsed-wave RF radiation at 400 MHz (SAR not given) for 6 minutes. The electric-field strength was 50 kV/m. No effects on the number of apoptotic cells or micronuclei were found. [The Working Group noted that interpretation of these findings was difficult due to the lack of SAR values and very short exposure times.]

Capri *et al.* (2004a) exposed human peripheral blood mononuclear cells to continuous-wave or GSM-modulated RF radiation at 900 MHz (average SAR, 70–76 mW/kg) for 1 hour per day, for 2 or 3 days. In general, no differences were detected in apoptosis – measured by means of annexin V-FITC staining – between exposed and sham-exposed cells, irrespective of whether or not the cells were treated with 2-deoxy-D-ribose, an inducer of apoptosis. In a similar study (Capri *et al.*, 2004b), the cells were exposed intermittently (10 minutes on, 20 minutes off) to RF radiation at 1800 MHz with three different GSM-modulation schemes (SAR, 1.4 or 2 W/kg) for 44 hours. No effects on apoptosis were observed from RF radiation alone or from RF radiation combined with the apoptosis-inducing agent, 2-deoxy-D-ribose.

Hook *et al.* (2004a) reported no effects on apoptosis, detected by use of the annexin V affinity assay, in human Molt-4 lymphoblastoid leukaemia cells exposed to RF radiation at 847.74 MHz as CDMA, 835.62 MHz as FDMA, 813.56 MHz as iDEN, or 836.55 MHz as TDMA signals, for up to 24 hours. The SARs were 3.2 W/kg for CDMA and FDMA, 0.0024 or 0.024 W/kg for iDEN, and 0.0026 or 0.026 W/kg for TDMA.

Gurisik *et al.* (2006) exposed human neuroblastoma SK-N-SH cells to RF radiation at 900 MHz (GSM; SAR, 0.2 W/kg) for 2 hours. Apoptosis was measured by means of propidium iodide/YO-PRO-1 staining. No differences were detected between sham-exposed and exposed samples.

Hirose *et al.* (2006) reported no effects on apoptosis, measured by the annexin V-FITC affinity assay, or on apoptosis-related gene expression, in human glioblastoma A172 or human IMR-90 fibroblasts exposed to RF radiation at 2142.5 MHz (SAR, 0.08–0.8 W/kg), with or without W-CDMA modulation, for 24–48 hours.

Joubert *et al.* (2006) studied apoptosis in human neuroblastoma SH-SY5Y cells exposed to GSM-modulated RF radiation at 900 MHz (SAR, 0.25 W/kg) or continuous-wave RF radiation at 900 MHz (SAR of 2 W/kg) for 24 hours.

No effects on apoptosis were detected, either immediately or 24 hours after exposure, with three different techniques, *viz.* 4′,6-diamino-2-phenylindole (DAPI) staining of nuclei, flow cytometry with double staining (TUNEL and propidium iodide), or measurement of caspase-3 activity by fluorometry.

Lantow *et al.* (2006c) reported no effects on apoptosis – measured with the annexin V-FITC assay – in human Mono Mac 6 cells exposed to 1800 MHz GSM-modulated RF radiation (SAR, 2.0 W/kg) for 12 hours, either alone or in combination with the apoptosis-inducing agents PMA or gliotoxin.

Merola *et al.* (2006) exposed human neuroblastoma LAN-5 cells to RF radiation at 900 MHz (GSM; SAR of 1 W/kg) for 24 or 48 hours. This exposure did not affect apoptosis, measured by an assay for caspase activation. In addition, RF-radiation did not enhance camptothecin-induced apoptosis.

Sanchez *et al.* (2006b) exposed human epidermal keratinocytes and fibroblasts to RF radiation at 900 MHz (GSM; SAR, 2 W/kg) for 48 hours. No alteration in apoptosis was detected in the annexin V/FITC affinity assay, while a very clear response was seen for UVB radiation, which was used as a positive control. In a subsequent study, Sanchez *et al.* (2007) exposed the same types of cell to RF radiation at 1800 MHz (GSM; SAR, 2 W/kg) for 2 hours. No effects on apoptosis were observed in the annexin V-FITC affinity assay.

Chauhan *et al.* (2007b) reported that apoptosis assessed by the neutral comet assay to detect DNA double-strand breaks was not affected in human TK6, HL-60, or Mono Mac 6 cells exposed to intermittent (5 minutes on, 10 minutes off) pulsed-wave RF radiation at 1900 MHz (SAR, 1, 10 W/kg) for 6 hours.

Höytö *et al.* (2008a) exposed human SH-SY5Y neuroblastoma cells to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg) for 1 or 24 hours under isothermal conditions, with or without the apoptosis-inducing agent menadione. No direct effects of RF radiation on apoptosis, or on menadione-induced apoptosis were observed in assays for caspase-3 activity and DNA fragmentation.

Human KB oropharyngeal epidermoid carcinoma cells were exposed to RF radiation at 1.95 GHz (SAR, 3.6 mW/kg) for 1, 2, or 3 hours. The exposure caused a time-dependent increase in apoptosis (45% after 3 hours), along with a 2.5-times decrease in the expression of the genes *RAS* and *RAF1* and in the activity of the proteins RAS and ERK-1/2. The overall results showed that RF radiation can induce apoptosis via inactivation of the ras–Erk survival-signalling pathway (Caraglia *et al.*, 2005) [the Working Group noted the lack of specific control of the temperature of the cells during the exposure periods in this study].

[The Working Group concluded that there was weak evidence that RF radiation induces apoptosis in human cells *in vitro*.]

(b) Other mammalian cells

See Table 4.15

(i) Stress response and ROS formation

Exposure of J774.16 mouse macrophages stimulated with γ-interferon and bacterial lipopolysaccharide to RF radiation at 835.62 MHz as FMCW, or to at 847.74 MHz as a CDMA signal (SAR, 0.8 W/kg) for 20–22 hours at 37 ± 0.3 °C did not alter the concentrations of intracellular oxidants (NO, glutathione disulfide), or activities of the enzymes CuZnSOD, MnSOD, catalase, or GSH-Px (Hook *et al.*, 2004b).

Zmyślony *et al.* (2004) reported an increase in cellular ROS production in rat lymphocytes coexposed to RF radiation and iron ions. The cells were exposed to continuous-wave RF radiation at 930 MHz (SAR, 1.5 W/kg) for 5 or 15 minutes in the presence of $FeCl_2$ (10 µg/ml). Intracellular ROS production, measured with the fluorescent probe 2′,7′-dichlorofluoresceindiacetate

Table 4.15 Effects of exposure to radiofrequency radiation in cultured mammalian cells *in vitro*

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Stress response and formation of reactive oxygen species					
Mouse, J774.16 macrophages	835.62 MHz (FMCW) or 847.74 MHz (CDMA); SAR, 0.8 W/kg; 20–22 h; 37.0 ± 0.3°C; stimulation with IFN and bacterial LPS	Oxidative stress evaluated by oxidant and antioxidant levels, oxidative damage and NO production. Oxidation of thiols measured by accumulation of GSSG. Cellular antioxidant defenses evaluated by SOD activity (CuZnSOD and MnSOD), CAT and GSH-Px activities.	No effect on parameters indicative of oxidative stress, levels of intracellular oxidants, accumulation of GSSG, or induction of antioxidant defences in IFN/LPS-stimulated cells. No toxicity was observed.		Hook *et al.* (2004b)
Hamster ovary HA-1 fibroblasts, Mouse C3H10T½, Human HeLa S3 cells	835.62 MHz (FMCW), 847.74 MHz (CDMA); SAR, 0.6 or 5 W/kg; 50–60 min, or 24 h; at 37.0 ± 0.28 °C, 36.9 ± 0.18 °C and 37.1 ± 0.28 °C for FDMA-, sham-, and CDMA-exposure, respectively.	DNA-binding activity of HSF – a necessary condition for induction of a heat-shock response – monitored with a gel-shift assay.	No increase in the DNA-binding ability of HSF after any exposure tested in any of the cell lines	A 10% increase was detectable after a 1 °C temperature increase	Laszlo *et al.* (2005)
Mouse L929 fibroblasts Human SH-SY5Y neuro-blastoma cells	872 MHz (CW or GSM); SAR, 5 W/kg; 1 h or 24 h.	Co-exposure (1 hour) with menadione (to induce ROS) or *t*-BOOH (to induce lipid peroxidation). Assessment of apoptosis (caspase3-like protease activity and DNA-fragmentation analysis) after 24 h exposure to RF	No effects of RF radiation alone. Menadione induced caspase-3 activity in L929 (not in SH-SY5Y) cells; lipid peroxidation was induced by *t*-BOOH in SH-SY5Y (not in L929) cells. Effects significant only for GSM-RF. Other end points not affected.	The positive findings may reflect effects that occur in cells sensitized by chemical stress.	Höytö *et al.* (2008a)
Mouse L929 fibrosarcoma cells	900 MHz (CW or GSM); SAR, 0.3 or 1 W/kg; 10 or30 min; with/without co-exposure to 500 µM of MX.	ROS formation measured by a fluorimetric method just after the exposure and at different times until 1 h after exposure	No effect of RF radiation (with or without MX) on formation of ROS		Zeni *et al.* (2007b)
Wistar rat; primary cortical astrocytes	900 MHz (CW or amplitude-modulated); electric field 10V/m; 5, 10, 20 min. Electric field at the sample position: 10 V/m.	Evaluation of intracellular ROS production, and of DNA damage (comet assay).	Increased ROS levels and DNA fragmentation after a 20-min exposure to AM-RF radiation. No effects of CW	Few details of experimental procedures; no temperature control	Campisi *et al.* (2010)
Rat lymphocytes	930 MHz (CW); SAR 1.5 W/kg; 5 or 15 min	Intracellular ROS measured with the fluorescent probe dichlorofluorescein diacetate (DCF-DA).	No effect on ROS formation		Zmyślony *et al.* (2004)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Rat, age 1–2 d, primary cortical astrocytes	1763 MHz (CDMA);average SAR, 2 or 20 W/kg; 30 min or 1 h.	Assessment of expression of HSPs and activation of MAPKs	No detectable effect on expression of HSP90, HSP70, HSP27; no change in MAPK phosphorylation, ERK1/2, JNK1/2, p38; no effect on TPA-induced MAPK phosphorylation	Temperature-control at 37 ± 0.2°C	Lee *et al.* (2006)
Newborn rat, primary cortical neurons	1800 MHz; average SAR 2 W/kg; (5 min on, 10 min off); 24 h	Melatonin was given 4 h before exposure to RF radiation. Immunostaining and HPLC analysis of 8-OHdG in mitochondria; number of copies of mtDNA; levels of mtDNA transcripts.	RF radiation induced a significant 2-fold increase in 8-OHdG in the mitochondria of neurons, and a reduction in the copy number of mtDNA and the amount of mtRNA transcripts. The effects could be partly reversed by pre-treatment with melatonin.		Xu *et al.* (2010)
Cell proliferation and cell cycle					
Mouse C3H 10T½ cells	835.62 MHz (CW or CDMA); average SAR, 0.6 W/kg; 13 h (short exposure), up to 100 h (long-term exposure)	Cell-cycle parameters (transit of cells through G1, G2, S phase; probability of cell division) evaluated immediately after cells were exposed for 3 h, or after 100 h exposure	No changes in cell-cycle parameters after exposure to either CW or CDMA	Controlled exposure and temperature	Higashikubo *et al.* (2001)
Mouse pre-neoplastic CLS1 mammary epithelial cells	Nanopulse electric-field strength of 18 kV/m; repetition rate 1–1000 kHz; up to 6 h. Cells cultured in the presence EGF (10 ng/ml) and insulin (10 µg/ml) as comitogens. After exposure, cells in all treatment groups were returned to the incubator for 72 h	After exposure, cells in all treatment groups were returned to the incubator for 72 h; cell growth and viability were assessed	No effect on CLS1 cell growth or viability during the subsequent culture period of 72 h after 0.25–3 h exposure to nanopulse radiation. Prolonged exposure (4–6 h) caused a significant increase in cell proliferation.	Radar-type signal. Increase in cell proliferation associated with MAPK activation in EGF-supplemented medium.	Sylvester *et al.* (2005)
Mouse embryonic stem cells	1720 MHz; SAR, 1.5 W/kg (5 min on, 30 min off); 6 or 48 h	Transcript levels of cell-cycle regulatory, apoptosis-related, and neural-specific genes and proteins; changes in proliferation, apoptosis, and cytogenetic effects (quantitative RT-PCR and comet assay).	No difference in rates of cell proliferation between exposed and sham-exposed cells		Nikolova *et al.* (2005)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Mouse HEI-OC1 immortalized auditory hair cells	1763 MHz (CDMA); SAR, 20 W/kg; 24 or 48 h	Cell cycle (flow cytometry), DNA damage (comet assay: tail length, tail moment) were evaluated. Stress response (HSP) and gene activation were analysed with Western blotting and DNA microarray (Affymetrix full mouse genome chips, 32 000 genes)	No cell-cycle change or DNA damage. No change in expression of HSP or in phosphorylation of MAPK; minimal changes in gene expression: only 29 genes down- or upregulated; no consistent group of functional categories.		Huang *et al.* (2008b)
Mouse CTLL-2 cytolytic T lymphocytes	2450 MHz (CW, PW); SAR, 25 or 50 W/kg (CW) and 5 W/kg (PW); 2 h	Effects of exposure on IL-2-dependent proliferation.	Consistent and statistically significant reduction in cell proliferation at low concentrations of IL-2.	Large sample size: 24 replicates per exposure group	Cleary *et al.* (1996)
Chinese hamster ovary (CHO) cells	27 MHz; SAR, 5 or 25 W/kg; 2 h	Cell-cycle alterations determined by flow-cytofluorometric DNA determinations	Significant SAR-dependent changes in cell-cycle progression, with maximum change occurring 3 d after the initial exposure		Cao *et al.* (1995)
Chinese hamster lung fibroblasts (V79 cells)	935 MHz (CW); SAR, 0.12 W/kg; 1, 2, 3 h	Microtubule protein morphology determined by immunocytochemistry immediately after exposure; cell proliferation examined by cell counts up to 5 d after exposure	No changes after 1 or 2 h exposure. After 3 h exposure, microtubules appeared morphologically grainy, comparable to those in colchicine-treated positive controls; no consistent change in proliferation.	Only one proliferation value decreased 3 d after exposure (but not at 4 and 5 d) in cells exposed for 3 h	Pavicic & Trosic (2008)
Chinese hamster ovary (CHO) cells	2450 MHz PW; SAR, 33.8 W/kg; 2 h; simultaneous exposure to adriamycin	Evaluation of percentage of first- and second-division mitotic cells after treatment with BrdU.	Exposure did not affect changes in cell progression caused by adriamycin.		Ciaravino *et al.* (1991)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Chinese hamster ovary CHO-K1 cell line	2450 MHz, continuous or intermittent; SAR, 0.05–200 W/kg; 2 h	Cell survival, growth and cell cycle (flow cytometry at 0–24 h) were determined	Exposure to CW RF radiation (SAR ≤ 100 W/kg) did not affect cell growth, survival, or cell-cycle distribution. At 200 W/kg, cell growth was suppressed and cell survival decreased. Exposure to intermittent RF radiation caused no significant effects. Exposures ≤ 200 W/kg (continuous) or ≤ 900 W/kg (intermittent) did not affect cell-cycle distribution.	Effects on proliferation due to temperature rise at SAR 50–200 W/kg	Takashima *et al.* (2006)
Chinese hamster V79 cells	7700 MHz, CW; power density, 30 mW/cm^2; 15, 30, 60 min	Incorporation of [^{3}H]thymidine and autoradiography	Decreased [^{3}H]thymidine incorporation immediately after exposure. Between 4 and 24 h after exposure, incorporation returns to control values; labelling index decreased after exposure, returned to normal after 24 h.	Normal incorporation rate is recovered within one cell generation; no information on temperature control	Garaj-Vrhovac *et al.* (1990)
Chinese hamster V79 cells	7700 MHz, CW; power density, 0.5, 10, 30 mW/cm^2; 10, 20, 30, 60 min	Cell survival assessed by colony-forming ability	Surviving fraction reduced in a time- and energy-dependent manner.	Exposure system kept under controlled temperature conditions at 22°C.	Garaj-Vrhovac *et al.* (1991)
Rat RBL-2H3 mast cells	835 MHz; estimated power density, 81 W/m^2; for 3 × 20 min/day for 7 days	Effects on cell proliferation, morphology and secretion	Increased [^{3}H]thymidine uptake and increased cell counts at days 6 and 7. Increased release of calcium	Exposure was variable across the chamber, based on temperature variation	Donnellan *et al.* (1997)
Transformed C6 rat glioma and normal primary glial cells (from d 17 rat embryos)	836.55 MHz (TDMA); power density 0.09, 0.9, 9 mW/cm^2; SAR, 0.15–59 mW/kg; 24 h	Monitoring of cell growth, DNA synthesis assay ([^{3}H]thymidine).	No difference in growth curves and doubling times between sham-exposed and exposed cells		Stagg *et al.* (1997)

Table 4.15 (continued)

Cell type	Exposure conditions	End-points	Results	Comments	Reference
Rabbit lens epithelial cells	2450 MHz (CW); intensity, 0.5–20 W/m^2; 2–8 h	Cell cycle (flow cytometry), cell viability (MTT assay); cell-cycle regulatory RNA and proteins (RT-PCR and Western blot).	Decreased number of cells in S-phase (decreased cellular replication) at exposures > 0.5 W/m^2 after 8 h	Inadequate description of the exposure conditions	Yao *et al.* (2004)
Apoptosis					
Mouse-embryo primary neurons and astrocytes	1900 MHz (GSM) from a mobile phone; SAR not given; 2 h, mode "on" (exposure) or "stand-by" (sham).	Expression of apoptosis-related genes studied by array analysis. Genes showing ≥ 35% decrease or increase further studied by real time RT-PCR.	Up-regulation of *Pycard*, *Casp*2, and *Casp*6 genes, both in "on" and "stand-by" modes, in neurons. *Pycard*, *Casp*2, *Casp*6, and *Bax* were upregulated in astrocytes, when cell phone in the "on""mode, but not in the "stand by" mode.	Cell phone placed over the culture dish; no dosimetry; no temperature control	Zhao *et al.* (2007a)
Mouse neuroblastoma N2a cells	935 MHz (GSM basic, GAM "talk", CW); SAR, 2 W/kg; 24 h. Cells were in proliferative and differentiated states.	Apoptosis assessed – up to 48 h after exposure – by fluorescence microscopy: annexin V, caspase activation, and *in situ* end-labelling.	No differences in apoptosis levels between exposed and sham-exposed proliferating or differentiated cells		Moquet *et al.* (2008)
Rat-embryo primary neurons	900 MHz (CW); SAR 2 W/kg; 24 h	Apoptosis assessed by condensation of DAPI-labelled nuclei, and TUNEL assay. Caspase-3 activity assessed by fluorimetry, and apoptosis-inducing factor (AIF) by immunofluorescence.	A highly significant increase in the percentage of apoptotic cells was seen at 24 h after exposure, compared with sham-exposed cells and cells incubated at 39 °C; no increase in caspase-3 activity, but increase in AIF labelling.	Results suggest caspase-independent mitochondrial apoptosis. Increase in temperature was 2 °C during exposure. Control experiments (no RF) with neurons at 39 °C did not show an increase in apoptosis	Joubert *et al.* (2008)

8-OHdG, 8-hydroxy-2′-deoxyguanosine; Asc, apoptosis associated speck-like protein containing a CARD; BrdU, bromodeoxyuridine; CDMA, code-division multiple access; CAT, catalase; CW, continuous wave; d, day; ERK1/2, extracellular signal-regulated kinases; FDMA, frequency-division multiple access; FM, frequency-modulated; GSH-Px, glutathione peroxidase; GSM, Global Systems Mobile communications; GSSG, glutathione disulfide; h, hour; HSF, heat-shock transcription factor; HSP, heat-shock protein; IFN, γ-interferon; JNK1/2, c-Jun N-terminal protein kinases; LPS, lipopolysaccharide; NO, nitric oxide; RF, radiofrequency; ROS, reactive oxygen species; RT-PCR, reverse-transcriptase polymerase chain reaction; SOD, superoxide dismutase; *t*-BOOH, *tert*-butylhydroperoxide

(DCF-DA), was elevated by 16.6% and 14.6%, respectively, at these time-points. Exposure to RF radiation alone did not affect ROS production.

Exposure of mouse C3H 10T½ cells and hamster ovary HA-1 fibroblasts to RF radiation at 835.62 MHz as FMCW signal, or at 847.74 MHz as CDMA signal (SAR, 0.6 or 5 W/kg) for 1 or 24 hours did not increase the DNA-binding activity of heat-shock transcription factor (Laszlo *et al.*, 2005).

Exposure of mouse L929 fibrosarcoma cells to continuous-wave or GSM-modulated RF radiation at 900 MHz (SAR, 0.3 or 1 W/kg) for 10 or 30 minutes, did not induce ROS formation by itself, or in combination with subtoxic concentrations of MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone, a by-product of water chlorination). In this study, MX strongly induced ROS formation (Zeni *et al.*, 2007b).

Höytö *et al.* (2008b) exposed mouse L929 cells to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg), for 1 hour or 24 hours, under isothermal conditions. To investigate possible effects of co-exposure with other agents, menadione was used to induce ROS, and *tert*-butylhydroperoxide (*t*-BOOH) was used to induce lipid peroxidation. No effects were observed after exposure to RF radiation only. Menadione-induced caspase-3 activity was significantly increased (but not in human neuroblastoma cells used in the same experiments) only by exposure to the GSM-modulated signal; *t*-BOOH-induced lipid peroxidation was not modified by RF radiation.

Lee *et al.* (2006) exposed cultures of primary astrocytes from newborn rats (aged, 1–2 days) to RF radiation at 1763 MHz as CDMA signal (average SAR, 2 or 20 W/kg) for 30 minutes or 1 hour, under temperature-controlled conditions at 37 ± 0.2 °C. RF radiation alone did not elicit a stress response and had no effect on TPA-induced MAPK phosphorylation.

Campisi *et al.* (2010) exposed cultures of primary astrocytes from newborn rats (age, 1–2 days) to continuous-wave or amplitude-modulated (50 Hz) RF radiation at 900 MHz (no SAR given; power density, 0.26 W/m^2), for 5, 10 or 20 minutes. There was an increase in ROS levels and DNA fragmentation (measured with the comet assay) after an exposure of 20 minutes to the amplitude-modulated RF radiation. With regards to the temperature of the cells during the exposure, the authors note that low-intensity RF radiation caused a minimal increase (0.03 °C) in temperature. [The publication gave few details about the experimental procedures.]

Xu *et al.* (2010) exposed primary cortical neurons from newborn rats to intermittent (5 minutes on, 10 minutes off) GSM-modulated RF radiation at 1800 MHz (average SAR, 2 W/kg) for 24 hours, and found significant increases ($P < 0.01$) in ROS production and in mitochondrial concentrations of 8-OHdG, and a reduction in copy numbers of mitochondrial DNA and mitochondrial RNA transcripts. These effects were partly reversed by treatment with melatonin 4 hours before exposure to RF radiation.

[The Working Group concluded that there was weak evidence that exposure to RF radiation activates stress response or ROS production in a variety of rodent cells *in vitro* under conditions not confounded by thermal effects.]

(ii) Cell proliferation and cell cycle

Exposure of Chinese hamster ovary (CHO) cells to pulsed-wave RF radiation at 2450 MHz (SAR, 33.8 W/kg) for 2 hours, did not affect cell-cycle progression, measured by analysis of first- and second-division mitotic cells after incorporation of bromodeoxyuridine. In the presence of adriamycin (given immediately before the exposure) RF radiation did not affect the cell-cycle progression induced by this drug (Ciaravino *et al.*, 1991).

Huang *et al.* (2008b) did not find evidence for the induction of cellular responses, including cell-cycle distribution, DNA-damage induction,

stress response and altered gene expression, in immortalized HEI-OC1 mouse auditory hair cells exposed to RF radiation 1763 MHz (CDMA; SAR, 20 W/kg) for 24 or 48 hours. [The Working Group noted that the choice of auditory hair cells was justified by the fact that auditory cells may be exposed to radiation from mobile phones.]

In V79 Chinese hamster lung fibroblasts, microtubule morphology – analysed by use of immunocytochemical methods – appeared modified following a 3-hour exposure to continuous-wave RF radiation at 935 MHz (SAR, 0.12 W/kg). No changes were noted after exposure for 1 or 2 hours (Pavicic & Trosic, 2008).

In V79 Chinese hamster cells exposed to continuous RF radiation at 7.7 GHz (SAR not given; power density, 30 mW/cm^2) for 15, 30, or 60 minutes, the incorporation of [^{3}H]thymidine decreased immediately after exposure. At longer time intervals after exposure, the incorporation of [^{3}H]thymidine increased and it returned to control values by 24 hours (Garaj-Vrhovac *et al.*, 1990b). In the same cells exposed to RF radiation under the same conditions with power densities of 0.5, 10, 30 mW/cm^2, the surviving fraction – assessed by colony-forming ability – was reduced in a time- and energy dependent manner (Garaj-Vrhovac *et al.*, 1991).

Cao *et al.* (1995) exposed CHO cells in different phases of the cell cycle to continuous-wave RF radiation at 27 MHz (SAR, 5 or 25 W/kg), for 2 hours. The cells were followed at sampling time-points up to 96 hours after exposure. Significant SAR-dependent changes in cell-cycle progression were observed, with the maximum change occurring at 3 days after exposure.

Cleary *et al.* (1996) exposed CTLL-2 mouse cytolytic cells to continuous-wave RF radiation at 2450 MHz (SAR, 5–50 W/kg), or to pulsed-wave RF radiation at 2450 MHz (SAR, 5 W/kg) for 2 hours. There was a decrease in cell proliferation (assessed by means of [^{3}H]thymidine incorporation) with continuous-wave, and an increase with pulsed-wave radiation. The effects were dependent upon the IL2 concentrations in the culture and the stage of the cell cycle.

Donnellan *et al.* (1997) exposed rat RBL-2H3 mast cells to RF radiation at 835 MHz (estimated power density, 81 W/m^2) for 20 minutes, three times per day for 7 days. Increased uptake of [^{3}H]thymidine and increased cell counts were observed at days 6 and 7, and an increase in the release of calcium was detected in the exposed group. [The exposure was variable across the exposure chamber based on temperature variations; eight samples were used for each group for analysis.]

Stagg *et al.* (1997) exposed rat primary glial cells and C6 glioma cells to RF radiation at 836.55 MHz as TDMA signal (SAR, 0.59, 5.9, 59 mW/kg) for 4 or 24 hours. A small but significant increase (P = 0.026) in the uptake of [^{3}H]thymidine was detected in C6 glioma cells at 5.9 mW/kg. In the other exposure groups no effects from exposure to RF radiation were observed ([^{3}H]thymidine uptake, cell growth).

Higashikubo *et al.* (2001) exposed mouse fibroblast (C3H 10T½) and human glioblastoma (U87MG) cells to RF radiation at 847.74 MHz as CDMA signal or at 835.62 MHz as TDMA signal (SAR, 0.6 W/kg) for up to 100 hours. No significant effects were found on cellular replication, as measured with the bromodeoxyuridine pulse-chase flow-cytometry method.

Takashima *et al.* (2006) exposed Chinese hamster ovary CHO-K1 cells to continuous-wave RF radiation at 2450 MHz (SAR, 0.05–200 W/kg) for 2 hours, or to intermittent RF radiation at 2450 MHz (average SAR, 50 or 100 W/kg) for 2 hours. Continuous-wave RF radiation at 200 W/kg decreased cell replication and cell survival. None of the other exposures showed an effect. [The temperature of the medium increased to 44.1 °C during exposure at a SAR of 200 W/kg).]

Yao *et al.* (2004) exposed replicates of rabbit-lens epithelial cells to continuous-wave RF radiation at 2450 MHz (no SAR given; power density,

0.1–2 mW/cm^2, for 8 hours at 25 °C. Cell viability was significantly reduced at power densities of 0.5 mW/cm^2 and higher. The numbers of cells in S-phase decreased and that of cells in G_0/G_1 phase increased – both significantly – at power densities ≥ 0.5 W/m^2. [The Working Group had some difficulty in understanding the discription of the exposure conditions in this study.]

Nikolova *et al.* (2005) exposed mouse embryonic stem cells to intermittent (5 minutes on, 30 minutes off) RF radiation at 1720 MHz (time-averaged SAR, 1.5 W/kg; during actual exposure, 12 W/kg) for 6 or 48 hours. No effects on the incorporation of bromodeoxyuridine were observed.

Sylvester *et al.* (2005) exposed mouse preneoplastic CL-S1 mammary epithelial cells to RF radiation as ultra-wide band pulses with an electric-field strength of 18 kV/m and a repetition rate in the range of 1–1000 kHz for up to 6 hours. No effect on CL-S1 cell growth or viability was observed after exposures of 0.25–3 hours. Exposure for 4 hours resulted in a significant increase in cell proliferation compared with untreated controls. There was no further increase at 5 or 6 hours.

[The Working Group concluded that the evidence that RF radiation has an effect on cell proliferation and cell cycle was weak.]

(iii) Ornithine decarboxylase activity (rodent and human cells)

Ornithine decarboxylase (ODC) is the first and rate-limiting enzyme in the polyamine biosynthesis pathway. Because polyamines are involved in the control of cell replication and differentiation, a change in cellular ODC activity is relevant to carcinogenesis. Tumour promoters such as TPA induce ODC activity, and a high level of ODC activity has been found in several premalignant conditions.

Byus *et al.* (1988) exposed Reuber H35 hepatoma, Chinese hamster ovary (CHO), and human 294 T melanoma cells to amplitude-modulated RF radiation at 450 MHz (SAR not geven; power density, 1.0 mW/cm^2) for 1 hour. A 50% increase in ODC activity was observed after exposure to RF radiation alone. In addition, ODC activity induced by TPA was further enhanced by exposure to RF radiation in H35 and CHO cells.

Litovitz *et al.* (1993) reported a 90% increase in ODC activity in murine L929 fibroblasts exposed to RF radiation at 915 MHz (SAR, 2.5 W/kg; amplitude-modulated at 55, 60, or 65 Hz) for 8 hours. A continuous-wave signal did not affect cellular ODC activity. Subsequent findings from the same laboratory (Litovitz *et al.*, 1997; Penafiel *et al.*, 1997) showed increased ODC activity in L929 cells exposed at 840 MHz (SAR, 2.5 W/kg) as a TDMA mobile-phone signal (burst-modulated at 50 Hz, with 33% duty cycle) for 2–24 hours. Also, signals with amplitude modulation at 60 Hz or 50 Hz induced ODC activity, whereas a signal modulated with speech, the signal of an analogue mobile phone, or a signal frequency modulated at 60 Hz, did not affect ODC activity. Various exposure times between 2 hours and 24 hours were used and the effect was most pronounced after exposure for 8 hours.

Desta *et al.* (2003), in an attempt to replicate the study of Penafiel *et al.* (1997), did not find any increase in ODC activity in murine L929 cells exposed to RF radiation at 835 MHz (SAR, < 1 W/kg; TDMA modulated) for 8 hours. In contrast, a decrease in ODC activity was observed at SARs of 1–5 W/kg. This decrease became statistically significant at SAR values > 6 W/kg, associated with a temperature increase of > 1 °C in the cell-culture medium.

In another replication study, Höytö *et al.* (2007) found no increase in ODC activity in L929 cells from two different sources using the same exposure system as Penafiel *et al.* (1997): a decrease in ODC activity was observed at the highest SAR used (6 W/kg). With a different exposure system and better temperature control

was used, a small increase in ODC activity was observed after 8 hours of exposure at 6 W/kg. This increase could be related to the temperature-control system, creating a temperature gradient in the cell cultures (lower temperature at the bottom of the cell culture). Höytö *et al.* (2006) reported no effects on ODC activity in L929 cells exposed to continuous-wave or GSM-modulated RF radiation at 900 MHz (SAR, 0.2 or 0.4 W/kg) for 2, 8, or 24 hours. ODC activity decreased after conventional heating (without exposure to RF radiation), consistent with the findings of Desta *et al.* (2003). Apparently, temperature differences of < 1 °C are sufficient to influence ODC activity.

Höytö *et al.* (2007b) also exposed L929 murine fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells, and rat primary astrocytes to continuous-wave and GSM-modulated RF radiation at 815 MHz (SAR, 1.5, 2.5 or 6 W/kg) for 2, 8 or 24 hours. A significant decrease in ODC activity was consistently observed in all experiments with rat primary astrocytes exposed to GSM-modulated or continuous-wave RF radiation at SARs of 1.5 or 6.0 W/kg. No effects were seen in the other cell lines.

Billaudel *et al.* (2009a) found no effects on ODC activity in L929 mouse fibroblasts exposed to RF radiation at 835 MHz, 900 MHz, or 1800 MHz as GSM or DAMPS-modulated signals (SAR, 0.5–2.5 W/kg) for 2–24 hours. The same authors reported that – consistent with the findings in murine cells – ODC activity was unaffected in human SH-SY5Y neuroblastoma cells exposed to GSM-modulated RF radiation at 1800 MHz, or DAMPS-modulated RF radiation at 835 MHz (SAR for both, 1 or 2.5 W/kg) for 8 or 24 hours (Billaudel *et al.*, 2009b).

[The Working Group concluded that there was moderate evidence that RF radiation alters ODC activity.]

(iv) Apoptosis

Rat embryo primary neurons were exposed to continuous-wave RF radiation at 900 MHz (SAR, 2 W/Kg) for 24 hours. Because the temperature increased by 2 °C during the exposure, a control experiment at 39 °C was included (without RF radiation). Apoptosis was measured with two different methods (staining of nuclei with 4′,6-diamino-2-phenylindole (DAPI) and analysis of DNA fragmentation with TUNEL-flow cytometry). With both techniques, a highly significant increase in the percentage of apoptotic cells was seen at 24 hours after exposure, compared with the sham-exposed cells and the cells incubated at 39 °C (Joubert *et al.* (2008).

Nikolova *et al.* (2005) exposed mouse embryonic stem cell-derived neural progenitor cells to intermittent (5 minutes on, 30 minutes off) GSM-modulated RF radiation at 1710 MHz (time-averaged SAR, 1.5 W/kg; during actual exposure, 12 W/kg) for 6 or 48 hours. No effects on apoptosis or on mitochondrial membrane potential were found.

Höytö *et al.* (2008a) exposed mouse L929 cells to 872 MHz continuous-wave or GSM-modulated RF radiation (SAR of 5 W/kg) for 1 or 24 hours under isothermal conditions. Menadione-induced apoptosis (tested by measuring caspase-3 activity) was increased in cells exposed to the GSM-modulated signal, but not in cells exposed to the continuous-wave signal. No effects were seen from RF radiation in the absence of menadione. As described earlier, no effects or RF radiation on apoptosis were observed in human cells in this same study.

Höytö *et al.* (2008b) exposed mouse L929 fibroblasts that had been stimulated with fresh medium, stressed by serum deprivation, or not subjected to stimulation or stress, to continuous-wave or GSM-modulated RF radiation at 872 MHz (SAR, 5 W/kg) for 1 hour under isothermal conditions. Increased apoptosis (tested by measuring caspase-3 activity) was

seen as a response to serum deprivation, but no consistent effects of exposure to RF radiation were found.

Joubert *et al.* (2007) studied apoptosis in rat primary cortical neurons exposed to GSM-modulated RF radiation at 900 MHz (SAR, 0.25 W/kg), or continuous-wave at 900 MHz (SAR, 2 W/kg) for 24 hours. No effects on apoptosis were detected, either just after the exposure or 24 hours later, with three different techniques, *viz*. 4′,6-diamino-2-phenylindole (DAPI) staining, flow cytometry with double staining (TUNEL and propidium iodide), or measurement of caspase-3 activity by fluorometry.

Zhao *et al.* (2007a) exposed cultured primary mouse embryonal neurons and astrocytes to 1900 MHz RF radiation from a working mobile phone (SAR not given) for 2 hours. The phone was placed with its antenna over the centre of the culture dish. During sham-exposures the phone was on "stand-by." Three apoptosis-associated genes (*Pycard,* encoding the Asc protein – apoptosis-associated speck-like protein containing a caspase-recruitment domain – *Casp2*, and *Casp6*) were upregulated in neurons, both after exposure and sham-exposure. In astrocytes the upregulation was observed in exposed cells only. In addition, the astrocytes – not the neurons – showed RF radiation-dependent upregulation of the *Bax* gene. [The Working Group noted the ill-defined exposure conditions in this study; see above.]

Moquet *et al.* (2008) exposed mouse neuroblastoma N2a cells to RF radiation at 935 MHz (SAR, 2 W/kg) for 24 hours, as GSM basic (amplitude-modulated), GSM "talk," and continuous-wave signal. No significant differences in levels of apoptosis were observed between exposed and sham-exposed cells.

[The Working Group concluded that there is weak evidence that RF radiation affects apoptosis in mammalian cells.]

4.5 Physical factors that affect interpretation of study results

4.5.1 Effects of critical RF-field parameters

(a) Modulation

There is evidence that modulation of the carrier waves of RF radiation can cause changes in biological processes that do not occur when the waves are not modulated. Examples of biological reactions to modulated RF radiation were clearly shown by Bawin *et al.* (1975), replicated by Blackman *et al.* (1979). For more examples and details, see the reviews by Blackman (2009) and Juutilainen *et al.* (2011).

(b) Power-intensity "windows"

Studies by Bawin *et al.* (1975, 1978) and Blackman *et al.* (1980) have characterized the power-density response in detail for the RF radiation-induced release of calcium ions from the chick brain ex vivo. Both groups observed regions of power density, termed "windows," in which the release of calcium ions was exposure-dependent, separated by regions that did not respond as a function of the power density of incident radiation. Subsequent reports by Dutta *et al.* (1984, 1989) revealed similar power-density windows of induced response in nervous system-derived cultures of human and animal cells, and Schwartz *et al.* (1990) observed windows of calcium-ion release from the frog heart ex vivo. This phenomenon appeared to be caused by the response characteristics of the particular biological preparations. The extensive characterization of exposure–response at 50, 147 and 450 MHz (amplitude-modulated, 16 Hz) in the chick brain showed that the windows could be aligned across carrier frequencies if one used the calculated electric-field strength at the tissue surface, rather than the incident power density (Joines & Blackman, 1980, 1981; Joines *et al.*, 1981; Blackman *et al.*, 1981, 1989). See reviews by Blackman (2009) and Belyaev (2010).

4.5.2 Frequency dependence and frequency windows

Effects of RF radiation are dependent on the frequency of the carrier wave. Differences in the response of human cells to GSM-type RF radiation were observed at frequency channels of 905 and 915 MHz, where the other conditions of exposure were the same (Belyaev *et al.*, 2009; Markovà *et al.*, 2010). Thus, it is important to know which difference in carrier frequency is acceptable to compare results from different studies.

The frequency-dependence of the effects of microwave radiation in different model systems and with different end-points measured has been reviewed (Grundler, 1992; Grundler *et al.*, 1992; Belyaev *et al.*, 2000; Belyaev, 2005, 2010). The effects of resonance-type microwave radiation were observed within multiple frequency-windows at intensity values well below those at which any thermal effects had been observed. The half-width of resonances and distance between them varied in dependence on the intensity of the RF radiation. Sharper and narrower resonances, and half-widths reaching at least 2 MHz were observed at the lower intensities.

4.5.3 Polarization

Different kinds of polarization were applied in the experimental studies discussed above: linear, left-handed circular, and right-handed circular polarization. It has been shown in many studies that biological effects are dependent upon polarization (Belyaev *et al.*, 1992a, c, d, 1993a, b; Shcheglov *et al.*, 1997; Ushakov *et al.*, 1999, 2006a; Belyaev & Kravchenko, 1994; Belyaev, 2010). For example, polarization should be taken into account when attempting to replicate the results of previous studies. For example, Lai & Singh (1996) used circular polarization, wheras linear polarization was applied in subsequent studies aimed at replicating their results, thus reducing sensitivity.

4.5.4 Dose and duration of exposure

While accumulated absorbed energy is measured as "dose" (dose rate multiplied by exposure time) in radiobiology, guidelines for exposures to RF radiation usually state power density or SAR (dose rate analogue) to define exposure. Several studies have analysed the relationship between dose and duration of exposure, with results suggesting that duration of exposure and dose may be important for cancer-relevant effects. In particular, prolonging the duration of exposure could compensate for the effects of a reduction in intensity.

Kwee & Raskmark (1998) analysed proliferation of human epithelial amnion cells exposed to RF radiation at 960 MHz, with SARs of 0.021, 0.21, or 2.1 mW/kg. These authors reported linear correlations between duration of exposure at 0.021 and 2.1 mW/kg and changes in cell proliferation, although no clear correlation was seen at 0.21 mW/kg.

Exposure of *E. coli* and rat thymocytes to RF radiation at power densities 0.01–1 mW/cm^2 resulted in significant changes in chromatin conformational state, if exposure was performed at resonance frequencies for 5–10 minutes (Belyaev *et al.*, 1992a, b; Belyaev & Kravchenko, 1994). Decreases in these effects caused by lowering the power density by an order of magnitude could be compensated for by a several-fold increase in the duration of exposure. At exposures longer than 1 hour, the same effect could be observed even at the lowest power density (Belyaev *et al.*, 1994).

4.5.5 Background fields of extremely low frequency (ELF)

Background ELF (1–300 Hz) fields vary between laboratories. Even within the same laboratory or the same RF exposure system, variations of up to 5 μT are not uncommon. Four studies investigated the influence of background

ELF fields on the effects of exposure to RF radiation: ODC activity in L929 cells (Litovitz *et al.*, 1997), hypoxia sensitization caused by long-term repeated exposures of chick embryos (Di Carlo *et al.*, 2002), spatial learning deficits in rats induced by microwave radiation (Lai, 2004), and DNA-damage induction in rat brain cells (Lai & Singh, 2005). In these studies, the effects caused by RF radiation were significantly reduced by imposing an ELF field of up to 5 μT.

4.5.6 Net static geomagnetic field

The static geomagnetic field (30–70 μT, depending on the location) may alter the cellular response to RF radiation (Belyaev *et al.*, 1994; Ushakov *et al.*, 2006b). Net static magnetic fields vary by location, even within the same laboratory and with the same exposure system, due to the ferromagnetic properties of laboratory equipment. For example, the resonance effects of microwave radiation on DNA repair and chromatin conformation in *E. coli* depend on the magnitude of the net static geomagnetic field at the site of exposure (Belyaev *et al.*, 1994; Ushakov *et al.*, 2006b).

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5. SUMMARY OF DATA REPORTED

5.1 Exposure data

This Monograph is concerned with non-ionizing radiation in the radiofrequency (RF) range of the electromagnetic spectrum, i.e. between 30 kHz and 300 GHz. The corresponding wavelengths – the distance between successive peaks of the RF waves – range from 10 km to 1 mm, respectively. Human exposure to RF radiation can occur from many different sources and under a wide variety of circumstances, including the use of personal devices (mobile phones, cordless phones, Wi-Fi, Bluetooth, amateur radios, etc.), occupational sources (high-frequency dielectric and induction heaters, broadcast antennas, high-power pulsed radars, and medical applications), and environmental sources (mobile-phone base stations, broadcast antennae). These multiple sources contribute to an individual's total exposure, with contributions varying by different characteristics, e.g. place of residence. The dominant sources of human exposure to RF radiation are near-field sources for workers, and transmitters operating on or in close vicinity to the body, such as hand-held devices, for the general population.

Electromagnetic fields generated by RF sources couple with the human body, which results in induced electric and magnetic fields and associated currents inside body tissues. The most important factor that determines exposure is the distance of the transmitter from the human body, within the main radiation beam. In a first approximation, the induced field strength is proportional to the time-averaged radiated power and inversely proportional to the distance from the source. In addition to distance, the efficiency of coupling and the resulting field distribution inside the body strongly depend on properties of the fields, such as frequency, polarization, distance from the antenna and direction of incidence, and on anatomical features of the exposed person, including height, posture, body mass index, shape of the head and associated structures such as the pinna (the outer ear), and dielectric properties of tissues. Induced fields within the body are highly non-uniform, with local hotspots and variations of several orders of magnitude. An important theme in studies on RF dosimetry is the focus on demonstrating compliance with exposure limits defined in terms of the localized and whole-body specific absorption rate (SAR) of energy. In recent years, measurement and simulation tools have been refined to allow exposure estimates in specific tissues or organs to be made for particular exposure scenarios, including those involving devices such as mobile phones.

While the number of mobile-phone subscriptions has been increasing rapidly around the world (4.6 billion subscribers in 2009), changes in mobile-phone technology have led to lower time-averaged RF power emitted from mobile phones used at present than those of previous generations. Of major interest to this *Monograph* is the exposure scenario in which mobile phones are held against the ear during a voice call. The

magnitude and spatial distribution of the ensuing SAR inside the brain depend on the design of a phone and its antenna, its position relative to the head, the anatomy of the head, how the hand holds the phone, as well as on the quality of the connection between the base station and the phone. GSM900/1800/PCS phones (Global System for Mobile communications/Personal Communications Service, operating at 900 or 1800 MHz) held next to the ear induce high spatial-averaged SAR values in the brain. This is because adaptive power control on average only reduces the output power to about 50% of its maximum during calls, but this would vary depending on the network software. The use of discontinuous transmission during voice calls would give a further 30% reduction in power. Analogue phones, which ceased to be used around the year 2000, produced still higher absorption of energy in the brain for two reasons: the handsets had higher output powers than modern phones, and the larger size of the handsets and antennae led to a more diffuse pattern of energy absorption in the head. Adaptive power control is much more effective with third-generation (3G) phone technologies, and this has led to a reduction of SAR in the brain by almost two orders of magnitude compared with that from GSM phones. The DECT (Digital Enhanced Cordless Telecommunications) phone is another widely used device that is held against the ear to make and receive voice calls. The average SAR in the brain from use of DECT phones is around five times lower than that measured for GSM phones.

The maximum spatial peak exposure to RF fields from mobile phones is very similar between different technologies. However, it may vary by up to a factor of 10 dependent on specific phone design. The spatial maximum exposure from cordless DECT phones is an order of a magnitude lower than that from mobile phones. Modulation and access schemes have also evolved to give a complicated output-power variation with time, while analogue technologies had a more constant pattern of output power.

Mobile-phone use is widespread in industrialized countries and rapidly growing elsewhere. Certain phone functions, such as text messaging, which involves considerably less exposure than voice calls, have become very popular among teenagers. Due to the closer proximity of the phone to the brain of children compared with adults, the average exposure from use of the same mobile phone is higher by a factor of 2 in a child's brain and higher by a factor of 10 in the bone marrow of the skull. In addition, dielectric properties of certain tissues, notably the bone marrow, change with age. The marrow progressively incorporates more fat, and the bone itself increases in thickness, hardens, and loses water over time. Both these tissues, therefore, have a higher conductivity in children than in adults and they receive a higher energy deposition from RF sources.

The use of hands-free kits lowers exposures from mobile phones to less than 10% of the value resulting from use at the ear, but it may increase exposure to other parts of the body. The rise in temperature inside the brain from use of a typical 3G mobile phone is small, approximately 0.1 °C or less.

Measures of mobile-phone use for epidemiological studies have historically relied on self-reporting, but recent validation studies among adults and children have demonstrated that there can be considerable random and systematic errors in the reported number of calls, the duration of calls, and the side of head where the phone is held during use. This is particularly problematic for epidemiological studies of cancer in humans, where information is needed on phone use many years in the past.

Assessments of household exposures to RF radiation often rely on spot measurements with a focus on burst activity, rather than on average values over time, which are better measures of RF exposure. Environmental sources are dominated

by possible RF exposures from being in close proximity to mobile-phone base stations, but actual measurements have shown that distance to a base station is not a good proxy for exposure, due to the considerable variability in characteristics of the antennae, and shielding and reflection of the waves. Typical exposures from rooftop- or tower-mounted mobile-phone base stations are lower by more than five orders of magnitude than those from GSM handsets. Exposures to the brain from television and radio stations are typically lower than those from base stations. Epidemiological studies of environmental RF sources need to include rigorous assessments of exposures to RF radiation, documented by direct measurements or through validated models.

Many occupations involve the use of sources of RF radiation at much higher power levels than those from mobile phones. For people exposed to high-power RF sources at work, cumulative energy deposition in the whole body may be much greater than from mobile-phone use, but the spatial peak SAR in the head will be less.

Tissue heating is the most firmly established mechanism for effects of RF radiation in biological systems. Although it has been argued that RF radiation cannot induce physiological effects at exposure intensities that do not cause a detectable increase in tissue temperature, except for reactions mediated by free radical pairs, it is likely that not all mechanisms of interaction between weak RF fields, with the various signal modulations used in wireless communications, and biological structures have yet been discovered or fully characterized.

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the Institute of Electrical and Electronics Engineers (IEEE) have developed guidelines for maximum human exposures to RF fields. These guidelines are designed to protect against adverse effects due to whole-body or partial body heating as a result of energy absorption above 100 kHz, and against nervous system effects at frequencies up to 10 MHz.

5.2 Human carcinogenicity data

The epidemiological evidence on possible associations of exposure to RF radiation with cancer comes from studies of diverse design that have assessed a range of sources of exposure: the populations included people exposed in occupational settings, people exposed through sources in the general environment, e.g. transmission towers, and people exposed through use of wireless (mobile and cordless) telephones. The most robust evidence is for mobile phones, the most extensively investigated exposure source. The general methodological concerns related to this evidence are covered in the introduction to Section 2 and are not reviewed again here.

As for any compilation of findings of epidemiological studies, interpretation of this evidence needs to give consideration to the possibility that observed associations reflect chance, bias, or confounding, rather than an underlying causal effect. The investigation of risk of cancer of the brain associated with mobile-phone use poses complex methodological challenges in the conduct of the research and in the analysis and interpretation of the findings.

5.2.1 Personal use of wireless telephones

(a) Tumours of the central nervous system: gliomas of the brain

One cohort study from Denmark and five case–control studies (from the USA, Finland, Greece, Sweden, and a multicentre international study) were judged by the Working Group to offer useful epidemiological information regarding associations between use of wireless phones and glioma. There are also several studies of time trends in occurrence of cancer of the brain in relation to the great temporal increase in mobile-phone use.

(i) Time-trend studies

It has been suggested that time trends in the incidence of cancer might reflect the impact of increasing use of mobile phones on cancer risk. In that regard, there have been some reports from various countries describing rates of brain cancer over time. In general, there has not been a documented and stable increase in rates since the advent of the mobile-phone era. However, the general absence of any documented increase in rates of tumours of the brain must be interpreted in light of the fact that most time trends were examined only before the early 2000s. However, any large risk associated with relatively recent exposure should have been detected in the studies conducted to date. Time trends in cancer of the brain have not shown evidence of a trend that would indicate a promptly acting and powerful carcinogenic effect of mobile-phone use.

(ii) Cohort study and early case–control studies

A large cohort study in the entire population of Denmark included mobile-phone subscribers with a median of 8 years of subscription. The study showed no excess risk of glioma, based on 257 exposed cases. Because of the reliance on subscription to a mobile-phone provider as a surrogate for mobile-phone use, this study involved considerable misclassification in exposure assessment.

Several case–control studies were carried out in a time window that was relatively early in the period of rising use. Three of these studies used self-reported histories of mobile-phone use, while a Finnish study made a link to mobile-phone subscription records. Effect estimates from these studies were generally too imprecise to make them informative.

(iii) The INTERPHONE study

The INTERPHONE study, a multicentre case–control study, comprised the largest investigation so far of mobile-phone use and brain tumours, including component studies of glioma, acoustic neuroma, and meningioma. The Working Group primarily considered the pooled analyses published in 2010 and 2011, rather than the findings as reported by site investigators or groups of investigators.

The pooled analysis of the INTERPHONE study on the risk of glioma in relation to use of mobile phones included 2708 cases of glioma and 2972 controls. Participation rates were 64% among cases of glioma and 53% among controls, with a wide variation in control participation rates among centres. For regular users, an overall reduced odds ratio (OR) was seen for glioma (OR, 0.81; 95% confidence interval [CI], 0.70–0.94); this was also observed in most study centres. Odds ratios of below unity were also found for all categories of time since start of use and of cumulative number of calls. The reason for these low odds ratios has not been established, but they probably reflect selection bias, at least in part. In terms of cumulative call time, all odds ratios were uniformly below unity for all deciles of exposure except for the highest decile (≥ 1640 hours of cumulative call time). For this exposure group, the odds ratio for glioma was 1.40 (95% CI, 1.03–1.89). Some other analyses of the same data also pointed to a possible association of mobile-phone use with risk of glioma, including the findings related to location of tumour (a higher odds ratio for tumours in the temporal lobe) and laterality of mobile-phone use (an apparently higher odds ratio in those who used a mobile phone on the same side of the head as the tumour). In an attempt to obviate the distortions that might have been generated by differential non-participation, an analysis was conducted with the lowest exposure decile as the reference; this showed a high odds ratio in the highest exposure decile. Recent reports presented findings based on methodological enhancements that derived dose indicators based on models applied to magnetic resonance imaging or computed tomography scans of the cases; these analyses in subsets of the INTERPHONE studies provide

additional insights into the patterns of risk of glioma associated with mobile-phone use.

The Working Group recognized several strengths of the INTERPHONE study, including its large sample size, the common core protocol, rapid case ascertainment, comprehensive data collection, and in-depth data analyses that included a wide variety of sensitivity and validation studies. However, the rather low participation rates may well have led to complicated and important patterns of selection bias.

In summary, in the INTERPHONE study there was no increased risk of glioma associated with having ever been a regular user of mobile phones. However, there were indications of an increased risk of glioma at the highest levels of cumulative call time, for ipsilateral exposures, and for tumours in the temporal lobe, but chance or bias may explain this increased risk.

(iv) Studies from Sweden

In 2011, Swedish investigators reported the findings of a pooled analysis of associations of mobile-phone and cordless-phone use and risk of glioma. Cases were ascertained from 1997 through 2003 in two waves. The Working Group considered the latest combined analysis of the study data. Both cases and controls were selected by use of population registries. A sequential approach by self-administered questionnaire and interview was used to collect information on the exposures and covariates of interest, including the use of mobile and cordless phones.

The analysis included 1148 cases with a diagnosis of glioma, and 2438 controls. When mobile-phone users were compared with people who reported no use of mobile or cordless phones, or exposure > 1 year before the reference date, an increased odds ratio was estimated (OR, 1.3; 95% CI, 1.1–1.6). The odds ratios increased progressively with increasing time since first mobile-phone use, and with increasing cumulative call time for the ordered categories of exposure duration (1–1000, 1001–2000, and > 2000 hours) as follows: 1.2 (95% CI, 0.98–1.4), 1.5 (95% CI, 1.1–2.1), and 2.5 (95% CI, 1.8–3.5), respectively. Ipsilateral use of the mobile phone was associated with higher risk. Further, there were similar findings in relation to the use of cordless phones.

The Working Group noted several strengths of the study. It was the only study to assess exposure to cordless phones. By using registries for case ascertainment and population-based controls, and by achieving high response rates, the investigators minimized the potential for selection bias. However, the possibility of information bias cannot be excluded, and specific validation studies were not carried out in this population.

(v) Comparison of the findings of INTERPHONE and the Swedish studies

Because these two studies represent the most robust evidence on risk of tumours of the brain associated with wireless-phone use, the Working Group compared the methods and findings of the two studies, drawing on comparisons made by the Swedish investigators – Hardell and colleagues – published in 2008 and 2010. The data were collected in overlapping calendar periods (1997–2003 for Hardell *et al.*, with separate analyses available for 2000–2003, and 2000–2004 for INTERPHONE) and had some shared design features, e.g. collection of exposure information via a comprehensive set of questions. The studies differ in their general design, a single population-based study in the case of Hardell *et al.* and a multicentre study based in case ascertainment through hospitals, although with backup case ascertainment through cancer registries and other sources. The INTERPHONE study is probably more affected by selection bias due to differential participation between cases and controls, while the findings of both studies are subject to information bias, probably comparable in directionality. The generally null findings in the two large case–control studies for meningioma speak against information bias providing a full explanation for the associations reported for glioma.

Overall, the Working Group reviewed all the available evidence with regard to the use of wireless phones, including both mobile and cordless phones, and the risk of glioma. Time trends were considered, as were several early case–control studies and one cohort study. The evidence from these studies was considered less informative than the results of the INTERPHONE study and the Swedish case–control study. While both of these are susceptible to bias, the Working Group concluded that these findings could not be dismissed as reflecting bias alone, and that a causal interpretation was possible.

(b) Other tumours of the central nervous system: acoustic neuroma

Several early case–control studies and one cohort study from Denmark found no association. The major sources of evidence for acoustic neuroma were essentially the same as for glioma, as was the general pattern of findings. The case numbers, however, were substantially smaller than for glioma. The study from Sweden provided positive results with estimates quite similar to those observed for glioma. The pattern of findings from the INTERPHONE study also paralleled that for glioma, with a decreased risk overall, and an indication of a possibly increased risk in the stratum with the longest cumulative call time. A case–case study in Japan published in 2011 also found some evidence of an increased risk of acoustic neuroma associated with ipsilateral mobile-phone use.

In considering the evidence on acoustic neuroma, the Working Group considered the same methodological concerns as for glioma, but concluded that bias was not sufficient to explain the positive findings, particularly those of the study from Sweden.

(c) Meningioma

For meningioma, the same two studies mentioned above provided the key evidence. Overall, in each, the findings generally indicated no increase in risk.

(d) Leukaemia/lymphoma

The Working Group reviewed results of four studies of mobile-phone use and leukaemia, including two cohort and two case–control studies. Two population-based case–control studies addressed lymphoma. The Working Group found the evidence to be insufficient to reach a conclusion as to the potential association of mobile-phone use and either leukaemia or lymphoma.

(e) Other malignancies

Evidence to date does not point to a causal association of mobile-phone use with the various additional malignancies addressed, including ocular or cutaneous melanoma, cancer of the testis, cancer of the breast, or tumours of the parotid gland. With the exception of cancer of the breast, all these malignancies have been investigated explicitly in one or more case–control studies. No increased risk was observed for the above-mentioned sites in the 2006 report of the cohort study of Danish mobile-phone subscribers.

5.2.2 Occupational exposure

(a) Tumours of the brain

Four independent case–control studies investigated the association of occupational exposure to RF radiation with risk of brain tumours through specific assessment of individual RF exposure. One study was based on death certificates, the others were population-based studies. Two nested case–control studies (one from the USA and another from Canada and France) also investigated this association. For

the category of highest exposure in each study – determined with the best exposure measure reported, i.e. some form of expert assessment of work history in each case – the odds ratios were above unity, but with wide confidence intervals, thus suggesting that occupational exposure to RF radiation might increase the risk of tumours of the brain. Only two studies (a nested case–control analysis from the USA and a case–control study from Australia) provided dose–response assessments, and neither of these showed more than moderate evidence of a dose–response relationship. In addition, only two studies examined the possibility of confounding by other occupational exposures. A study from Germany adjusted the odds ratios for exposure to ionizing radiation and a study from the USA, based on death certificates, evaluated the sensitivity of the observed positive association of exposure to RF radiation with cancer of the brain with respect to confounding with known coexposures: solder fumes, lead and organic solvents. The observed odds ratio of 1.7 (95% CI, 1.1–2.7) for classification of RF exposure based on expert assessment decreased to 1.4 (95% CI, 0.7–3.1) when men exposed to solder fumes and lead were excluded from the exposed group, and dropped further to 0.4 when those exposed to organic solvents were also removed (although only two exposed cases and five exposed controls were left in the analysis). Chance and/or confounding cannot be ruled out as likely explanations for the observed association between occupational exposure to RF radiation and cancer of the brain.

Eight cohort studies (including the two nested case–control studies mentioned above) and a Polish cross-sectional study examined the relationship between occupational exposure to RF radiation and risk of tumours of the brain. Relative risks for the categories of highest exposure in all but three of the studies were close to or below unity. Among the three exceptions, one study from Italy was based on only one death from cancer of the brain; the cross-sectional study from Poland showed a relative risk of 1.91 (95% CI, 1.08–3.47) but had methodological limitations that could explain the apparent increase in risk; and an American study had only a weakly increased relative risk (OR, 1.39; 95% CI, 0.93–2.00). On balance, therefore, the cohort studies did not suggest a positive association between exposure to RF radiation and cancer of the brain. Their exposure measures, however, were generally of less quality than those in the case–control studies.

While the association of exposure to RF radiation with cancer of the brain has been examined in a substantial number of studies, exposure misclassification and insufficient attention to possible confounding limit the interpretation of the findings. Thus, there is no clear indication of an association of occupational exposure to RF radiation with risk of cancer of the brain.

(b) Leukaemia/lymphoma

Seven cohort studies and one cross-sectional analysis examined the relationship between occupational exposure to RF radiation and risk of lymphoma and leukaemia. Most studies were based on small numbers of cases and limited exposure assessments. Increased standardized mortality ratios (SMRs) were seen for lymphomas and some leukaemias in a study of radio amateurs in the USA, but there was no association with an exposure-level surrogate (licence class). A substantially increased risk was also seen among Belgian military personnel who had worked with moveable radar, based on 11 cases, but exposure to RF radiation was not characterized individually and may have been confounded by ionizing radiation. In addition, follow-up of the cohort was problematic. The largest and most informative study was that of male United States navy veterans of the Korean War. Increased relative risks for leukaemia (in particular, acute myeloid and acute non-lymphocytic leukaemia) were seen among subjects with the highest compared with the lowest exposure. The highest odds ratio

was seen among technicians in aviation electronics, judged by the authors to be those with highest potential exposure. There was, however, no adjustment for potential confounders.

In summary, while there were weak suggestions of a possible increase in risk of leukaemia or lymphoma associated with occupational exposure to RF radiation, the limited exposure assessment and possible confounding make these results difficult to interpret.

(c) Other malignancies

Studies of occupational groups with potential exposure to RF radiation have addressed several additional types of malignancy including uveal melanoma, and cancers of the testis, breast, lung, and skin. The Working Group noted that these studies had methodological limitations and the results were inconsistent.

5.2.3 Environmental exposure

(a) Cancer of the brain

Ecological studies and case–control studies have been carried out to investigate potential associations of brain cancer with RF emissions from transmission antennae. These studies are generally limited by reliance on measures of geographical proximity to the antennae as an exposure surrogate. Substantial exposure misclassification is unavoidable.

Taken together, the ecological studies do not suggest a positive association between RF emissions from fixed transmission sources and cancer of the brain.

There have been five case–control studies of environmental exposure to RF radiation and risk of cancer of brain. Cohort studies have not been reported. In all of the case–control studies, exposure estimation was based on residential proximity to RF-transmitter antennae. Two of these studies used estimates of exposure based on recorded locations of subjects' residences relative to recorded locations of AM radio-transmitters or mobile-phone base-station antennae. Neither found convincing indications of an increase in risk of brain cancer with increasing estimated exposure to RF radiation. A hospital-based study from France depended on subjects' recall of the proximity of their residence to a mobile-phone base station and found no evidence of an increased risk with closer proximity. However, the hospital-based controls may not represent exposure in the general population. The fourth study assessed proximity of subjects' beds to base stations of DECT cordless phones in the home. It found a weak and imprecise increase in risk of brain cancer associated with sleeping near a base station. Another study found high risks for brain, breast and other cancers associated with the place of residence where the highest power density from a nearby base-station antenna was measured, but the results were imprecise and based on only a few cases. Together, these studies provide no indication that environmental exposure to RF radiation increases the risk of brain tumours.

(b) Leukaemia/lymphoma

Ecological studies in which distance was taken as a proxy for exposure consistently showed a pattern of increased risk of adult and childhood leukaemia with closer proximity to the exposure source, while studies that used analytical designs and better exposure assessments (e.g. measured and modelled) showed no increased risk. In adults, the evidence of an association indicating increased risk was weak at most, and effect estimates were generally imprecise. There was no evidence of an increased risk of childhood leukaemia. Consequently, from the limited data available no conclusions could be drawn on the risk of leukaemia or lymphoma from environmental exposure to RF radiation.

(c) Other malignancies

The Working Group identified five studies that addressed other malignancies and environmental exposure to RF radiation, and found the available evidence uninformative.

5.3 Animal carcinogenicity data

Four classes of cancer bioassays in animals were reviewed and assessed by the Working Group. These studies involved a variety of animal models, exposure metrics, durations of exposure, and other criteria on which the evaluation of carcinogenicity was based.

Seven two-year cancer bioassays of RF radiation were reported, two in mice and five in rats; six studies were performed to examine the effects of exposure to mobile-phone RF metrics, and one study involved exposure to pulsed RF radiation. When compared with sham controls, no statistically significant increases in the incidence of benign or malignant neoplasms at any organ site were identified in animals exposed to mobile-phone RF radiation in any study. In the study with exposure to pulsed RF radiation, an increased incidence of total malignant tumours (all sites combined) was observed in rats; however, the Working Group considered this finding to be of limited biological significance since it resulted from pooling of non-significant changes in tumour incidence at several sites. Exposure to RF radiation did not increase total tumour incidence in any of the other six studies that were evaluated. The Working Group concluded that the results of the 2-year cancer bioassays provided no evidence that long-term exposure to RF radiation increases the incidence of any benign or malignant neoplasm in standard-bred mice or rats.

The Working Group evaluated twelve studies that used four different tumour-prone animal models; two of these studies demonstrated an increased incidence of tumours in animals exposed to RF radiation. The first study with positive results demonstrated an increased incidence of lymphoma in *Eμ-Pim1*-transgenic mice exposed to GSM mobile-phone RF radiation at 900 MHz; however, two subsequent studies by other investigators using the same model system failed to confirm this finding. In the second study with positive results, an increased incidence of tumours of the mammary gland was observed in C3H/HeA mice exposed to RF radiation at 2450 MHz; although two later studies using the same exposure metric did not confirm this finding, these follow-on studies were performed at lower levels of exposure. The Working Group concluded that the results of studies in three tumour-prone animal models (the *Eμ-Pim1* mouse model of lymphoma, the AKR mouse model of lymphoma, and the *Patched1*$^{+/-}$ mouse model of brain cancer) do not support the hypothesis that the incidence of tumours in the brain or lymphoid tissue would increase as a result of exposure to RF radiation.

The Working Group evaluated 16 studies of initiation and promotion that were performed with animal models of tumorigenesis in skin, mammary gland, brain, and lymphoid tissue. None of the five studies in models of skin cancer and none of the six studies in models of brain cancer showed an association with exposure to RF radiation. One of four studies with the model of mammary-gland tumour in Sprague-Dawley rats gave positive results; the other three studies – one with a nearly identical protocol – did not show an association, although they used the same experimental model and the same conditions of exposure to RF radiation. Likewise, the study with the model of lymphoma was negative. The Working Group concluded that the evidence from these studies of initiation and promotion failed to demonstrate a consistent pattern of enhancement of carcinogenesis by exposure to RF radiation in any of the tissues studied.

The Working Group evaluated six co-carcinogenesis studies involving five different animal models. Four positive responses were reported.

Two studies giving positive results, one in Wistar rats continuously exposed to drinking-water containing MX – a by-product of water disinfection – and another study in pregnant B6C3F$_1$ mice given a single dose of ethyl-nitrosourea, involved exposures to mobile-phone RF radiation at 900 and 1966 MHz, respectively. The other two studies with positive results involved coexposure of BALB/c mice to RF radiation at 2450 MHz and benzo[*a*]pyrene. Although the value of two of these studies was weakened by their unknown relevance to cancer in humans, the Working Group concluded that they did provide some additional evidence supporting the carcinogenicity of RF radiation in experimental animals.

5.4 Other relevant data

The data to evaluate the mechanisms by which RF radiation may cause or enhance carcinogenesis are extensive and diverse. Studies in humans from occupational cohorts, mobile-phone users and controlled exposures in experimental settings provide information on effects in various tissues, including blood and brain. Studies in animals have been focused on a variety of organs and tissues. Assays *in vitro* in human cells, other mammalian cells, and cells from other organisms provide the largest set of data from which to evaluate mechanisms. Many studies were confounded by significant increases in the temperature of the cells, leading to thermal effects that could not be dissociated from non-thermal RF-induced changes. The conclusions presented in this section for results *in vivo* and *in vitro* pertain only to those studies for which the Working Group concluded that thermal confounding did not occur.

5.4.1 Genetic and related effects of exposure

Multiple studies in humans were conducted on the possible genetic damage associated with exposure to RF radiation. Most of these studies were of occupational exposure and the others evaluated mobile-phone users. Several common exposures to the general population that are likely to be confounders were generally not considered, including tobacco use and age. In addition, other occupational exposures that might have contributed to the findings were rarely discussed. Most of the occupational studies that suggested a positive association of the effect with exposure to RF radiation involved workers from the same facility, included small numbers of subjects, and provided no indication of the extent to which the same individuals were sampled in multiple studies. Virtually all the large studies did not show an association with exposure to RF radiation, for any type of genetic damage. Finally, there were methodological flaws and weaknesses in reporting in many studies, including the failure to actually measure exposure to RF radiation, the use of small numbers of cells for evaluating genetic damage, the failure to use proper controls while culturing cells, incomplete reporting, and improper interpretation of results.

A few studies in *Drosophila* that addressed mutagenicity after exposure to RF radiation gave negative results.

Approximately half of the laboratory studies of genetic damage in mammalian systems, generally rats and mice, had limitations related to reporting on the exposure system, small sample sizes and exposures that induced thermal effects, or that were so low as to be no challenge to the animals. Of the remaining studies, many were satisfactory and of comparable quality, but showed contradictory results. Some were attempts to repeat original laboratory findings. Also these studies provided mixed and sometimes contradictory results. Some of the discrepancies could be due to differences in species or

exposure conditions, but others were in direct contrast.

Roughly half of the studies of human cells *in vitro* were done in lymphocytes cultured from the blood of donors. Short-term, high-intensity exposures to RF radiation resulted in consistently positive results for DNA damage, but the Working Group felt that thermal effects were the likely cause of these effects. A large number of studies on DNA strand breaks and the studies on sister chromatid exchange generally gave negative results. Exposures to RF radiation in the non-thermal range also generally gave negative results.

The remaining in-vitro studies with human cells and the in-vitro studies with non-human cells also involved short-term, high-intensity exposures that consistently gave positive results for DNA damage. The Working Group considered that these results were likely due to thermal effects. There were acceptable reports showing both positive and negative results in the remaining studies with exposures in the non-thermal range. In addition, studies showing aneuploidy and spindle disturbances in human-hamster hybrid A_L cells, and studies at low exposures showing DNA single-strand breaks were of concern. While RF radiation has insufficient energy to produce these types of direct genetic damage, other changes such as oxidative stress and production of reactive oxygen species may explain these results.

The remaining few studies that gave positive results for genetic damage at lower doses could not be replicated after multiple attempts in different laboratories, raising serious questions regarding the original findings. A single study showing altered microtubule structures at low exposures remains a concern.

Overall, the Working Group concluded that there was weak evidence that RF radiation is genotoxic, and no evidence for the mutagenicity of RF radiation.

5.4.2 Reaction of the immune system after exposure

Several studies assessed the effects of exposure to RF radiation on indicators of immune function in humans. In two studies, increased concentrations of some immunoglobulins (Ig) and changes in numbers of lymphocytes (T8, natural killer [NK] cells) were observed in blood samples from radar operators and workers at television-transmission stations, but the results were variable and the alterations seemed to be within the normal variation. Two studies among workers exposed to very high frequency RF radiation showed a significant increase in IgG and IgM, and a higher number of NK cells, respectively. Patients with atopic eczema dermatitis showed an increase in allergen-provoked production of IgE when they had been exposed to RF radiation from a mobile phone. Many of these studies used small numbers of subjects and generally did not control for possible confounders.

The available evidence from numerous experimental studies *in vivo* that aimed to assess effects of short-term and prolonged low-level exposure to RF radiation on function and status of the immune system, clearly indicates that various shifts in number and/or activity of immunocompetent cells are possible. However, in some cases the same lymphocyte functions are reported to be weakened or enhanced in different single experiments, despite exposures to RF radiation at similar intensities and under similar exposure conditions. Short-term exposure to weak RF fields may temporarily stimulate certain humoral or cellular immune functions, while prolonged irradiation inhibits the same functions. Thus, even though there are indications that changes are occurring, the relevance of these observations in relation to carcinogenicity is unclear.

The effects of RF radiation on various types of human lymphocytes *in vitro* are variable and depend on the mitotic state of the cells during

exposure. A difference was reported between the effects of exposure to continuous-wave and pulsed-wave RF radiation, the latter preferentially stimulating the immunogenic and pro-inflammatory activity of monocytes. Many of these studies had weaknesses in the description of experimental procedures and from lack of detail on dosimetry.

Overall, the Working Group concluded that there was insufficient evidence to determine that alterations in immune function induced by exposure to RF radiation affect carcinogenesis in humans.

5.4.3 Effects on genes, proteins and signalling pathways

No studies assessing gene expression in humans exposed to RF radiation were identified, and only one pilot study assessed protein changes in exposed human subjects.

Nearly 30 studies investigated gene/protein changes in rodents exposed to RF radiation. Many of these studies were unreliable due to deficiencies in the exposure system or methodological shortcomings. The data from the remaining studies are limited and present mixed results with no consistent pattern of response.

A large number of studies have assessed the ability of RF radiation to affect gene/protein expression and protein activation in human-derived cell lines *in vitro*. The majority of studies assessing effects of RF radiation on expression and activity of heat-shock proteins reported no effect. A limited number of studies assessed the ability of RF radiation to influence the activity of signal-transduction pathways in human cells *in vitro*. Three studies found changes in MAPK signalling, while another did not. The role of reactive oxygen species in mediating these responses is unclear.

A total of 16 studies used high-throughput genomics/proteomics approaches to evaluate the effect of exposure to RF radiation on human cell lines *in vitro*. Many of these studies had serious methodological shortcomings related to poor exposure conditions, inadequate statistical analysis, and lack of validation of alternative approaches. The remaining data were limited with no consistent pattern of response, but some studies demonstrated changes in both gene and protein expression, for some proteins in some cell lines.

On the basis of the above considerations, the Working Group concluded that data from studies of genes, proteins and changes in cellular signalling show weak evidence of effects from RF radiation, but did not provide mechanistic information relevant to carcinogenesis in humans.

5.4.4 Other mechanistic end-points

Several potential changes resulting from exposure to RF radiation are summarized here. With the exception of changes in cerebral blood flow, many of the other studies reviewed by the Working Group provided conflicting, negative or very limited information, which made it difficult to draw conclusions, especially in relation to carcinogenesis. These studies focused on electrical activity in the brain, cognitive function, general sensitivity to RF radiation and alterations in brain biochemistry. Even though the relationship between alterations in cerebral blood flow during exposure to RF radiation cannot be directly related to carcinogenesis, the Working Group concluded that the available data were sufficiently consistent to identify them as important findings.

Some studies were conducted in experimental animals to explore the possibility that exposure to RF radiation *in vivo* may induce the production of reactive oxygen species in multiple organs, most frequently brain, but also kidney, liver and eye. Markers of oxidative stress included increases in the concentration of malondialdehyde (related to lipid peroxidation) and nitric oxide, enhanced activities of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and pro-oxidant enzymes, and reductions in

glutathione. Many of these studies are weakened by methodological shortcomings in design, such as absence of sham-exposed or cage-control groups, use of mobile phones as the exposure source, and lack of dosimetry.

A few studies in human cells *in vitro* evaluated the possible role of exposure to RF radiation in altering levels of intracellular oxidants or activities of antioxidant enzymes. One study showed a marginal effect, while other studies demonstrated an increase in activity with increasing exposures. There were not enough studies to make a reasonable assessment of the consistency of these findings. Additional studies addressed this issue in in-vitro systems with non-human cells. While most of these did not find changes, one study evaluated the formation of DNA adducts from reactive oxygen species (8-hydroxy-deoxyguanosine) and was able to demonstrate reversal of this effect by melatonin. While the overall evidence was inconclusive, the results from in-vitro studies with animal models raise some concern.

Overall, the Working Group concluded that there was weak evidence that exposure to RF radiation affects oxidative stress and alters the levels of reactive oxygen species.

Numerous studies have assessed the function of the blood–brain barrier in rodents exposed to RF radiation at various intensities. Consistent results from one laboratory suggest an increase in the permeability of the blood–brain barrier, but the majority of the studies, many of which aimed at replicating published results, failed to observe any effect on this point from exposure to either continuous or pulsed RF radiation. The evidence that exposure to RF radiation alters the blood–brain barrier was considered weak.

A few studies dealt with alterations induced by RF radiation in cell differentiation or induction of apoptosis in the brain or other organs. While most of the studies showed an association, the Working Group was not convinced that these data were of sufficient scientific rigour to assess apoptotic effects in these organs. An additional 14 studies focused on apoptosis in cultured human cells. Only two studies demonstrated an increase in apoptosis: one compared the results observed in treated cells with controls that were not subject to the same conditions as the exposed cells, while thermal effects may have had an impact in the other study. Finally, other in-vitro studies with non-human cells gave essentially negative results, with the exception of one study that demonstrated mixed results. The evidence that exposure to RF radiation alters apoptosis was considered weak.

Multiple assays *in vitro* were conducted to test proliferation of primary cells or established cell lines by analysis of cell-cycle progression and thymidine uptake, after exposure to various intensities of RF radiation at various time intervals. Many of these studies used small sample sizes and description of experimental details was lacking in several cases. Studies with positive results showed increases and decreases in cellular replication, and no consistent pattern could be discerned. The evidence that RF radiation alters cellular replication was considered weak.

Ornithine decarboxylase is an enzyme involved in the metabolism of polyamines, which are critical components of cellular replication and differentiation processes. The activity of this enzyme was the object of several studies *in vitro* in human and animal cells exposed to GSM900 and GSM1800 signals. Some of these studies showed significantly increased ornithine decarboxylase activity. The result of one study suggested that ornithine decarboxylase activities may be reduced. It was unclear how these changes in activity relate to human cancer. There was weak evidence from in-vitro studies that exposure to RF radiation alters ornithine decarboxylase activity.

The evidence that exposure to RF radiation, at intensities below the level of thermal effects, may produce oxidative stress in brain tissue and may affect neural functions was considered weak.

6. EVALUATION

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of radiofrequency radiation. Positive associations have been observed between exposure to radiofrequency radiation from wireless phones and glioma, and acoustic neuroma.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of radiofrequency radiation.

6.3 Overall evaluation

Radiofrequency electromagnetic fields are *possibly carcinogenic to humans (Group 2B).*

6.4 Rationale for the evaluation of the epidemiological evidence

The human epidemiological evidence was mixed. Several small early case–control studies were considered to be largely uninformative. A large cohort study showed no increase in risk of relevant tumours, but it lacked information on level of mobile-phone use and there were several potential sources of misclassification of exposure. The bulk of evidence came from reports of the INTERPHONE study, a very large international, multicentre case–control study and a separate large case–control study from Sweden on gliomas and meningiomas of the brain and acoustic neuromas. While affected by selection bias and information bias to varying degrees, these studies showed an association between glioma and acoustic neuroma and mobile-phone use; specifically in people with highest cumulative use of mobile phones, in people who had used mobile phones on the same side of the head as that on which their tumour developed, and in people whose tumour was in the temporal lobe of the brain (the area of the brain that is most exposed to RF radiation when a wireless phone is used at the ear). The Swedish study found similar results for cordless phones. The comparative weakness of the associations in the INTERPHONE study and inconsistencies between its results and those of the Swedish study led to the evaluation of *limited evidence* for glioma and acoustic neuroma, as decided by the majority of the members of the Working Group. A small, recently published Japanese case–control study, which also observed an association of acoustic neuroma with mobile-phone use, contributed to the evaluation of *limited evidence* for acoustic neuroma.

There was, however, a minority opinion that current evidence in humans was *inadequate*, therefore permitting no conclusion about a causal association. This minority saw inconsistency between the two case–control studies and a lack of exposure–response relationship in the INTERPHONE study. The minority also pointed to the fact that no increase in rates of glioma or acoustic neuroma was seen in a nationwide Danish cohort study, and that up to now, reported time trends in incidence rates of glioma have not shown a trend parallel to time trends in mobile-phone use.

GLOSSARY

Antenna: Device that serves as a transducer between a guided wave (e.g. via a coaxial cable) and a free space wave, or *vice versa*. It can be used either to emit or to receive a radio signal.

Base station: Wireless communications station installed at a fixed location and used to transmit and receive radio signals to and from mobile-phone users. Also used for DECT phones at home.

Cell phone: See "Mobile phone".

Cellular radio network: Fixed infrastructure comprising multiple base stations deployed across a wide geographical area such that mobile-phone users are able to communicate via the base stations, with the radio signals associated with their calls being transmitted from one base station to another as the users move across cell boundaries.

Conductivity: The ratio of the conduction-current density in a medium to the electric field strength. The unit of conductivity is siemens per metre (S/m).

Cordless phone: (DECT, portable phone) A wireless telephone that communicates via radio waves with a base station connected to a fixed telephone line, usually within a limited range of its base station. The base station is on the premises of the owner, and attached to the wired telephone network in the same way as a corded telephone.

DECT phone: See "Cordless phone"

Effective radiated power (ERP) or **equivalent radiated power:** is a standardized theoretical measurement of radiofrequency (RF) energy using the SI unit watts, and is determined by substracting system losses and adding system gains. ERP is similar to EIRP (see below), but may use some other reference antenna than an isotropic antenna, e.g. a half dipole.

Electric-field strength (E): Magnitude of a field vector at a point that represents the force (F) on a small test charge (q) divided by the charge:

$$\vec{E} = \frac{\vec{F}}{q}$$

The magnetic field strength is expressed in units of volt per metre (V/m).

Equivalent isotropically radiated power (EIRP) or **effective isotropically radiated power**: The amount of power that a theoretical isotropic antenna (which evenly distributes power in all directions) would emit to produce the peak power density observed in the direction of maximum antenna gain. EIRP can take into account the losses in transmission line and connectors and includes the gain of antenna. The EIRP is often expressed in terms of decibels over a reference power emitted by an isotropic radiator with an equivalent signal strength. The EIRP allows comparisons between different emitters regardless of type, size or form. From the EIRP, and with knowledge of a real antenna's gain, it

is possible to calculate real values for power and field strength.

Equivalent plane-wave power density (plane-wave equivalent power density) (S): A commonly used term associated with any electromagnetic wave, equal in magnitude to the power density of a plane wave having the same electric- (E) or magnetic- (H) field strength. Specifically, the normalized value of the square of the electric- or the magnetic-field strength at a point in the near field of a radiating source. The unit of equivalent plane-wave power density (according to the International System of Units, SI) is the watt per square metre (W/m^2) and is computed as follows:

$$S = \frac{|E|^2}{\eta} = \eta |H|^2$$

where:

E and H are the root-mean-square (rms) values of the electric- and magnetic-field strengths, respectively

η is the wave impedance (≅ 377 ohms in free space).

Note that most field-survey equipment uses this relationship, although it does not apply to the near field. In case of exposure assessment, the independent measurement of E *rms* (or $|E|^2$) and H *rms* (or $|H|^2$) is preferred.

Synonym: **equivalent plane-wave power flux density.**

Far-field region and near-field region: The far-field region is defined when the fields can be well approximated by the radiating fields, i.e. the E-field vector is perpendicular to the H-field vector, and both are orthogonal to the direction of propagation whereby the ratio of the amplitudes of the E- and H-fields is 377 ohm.

The near-field region is when the above conditions are not met, i.e. when the field is dominated by reactive field components.

Frequency and wavelength: The intensity of electric and magnetic fields can vary periodically over time and space, following a sinusoidal function. In the time domain, the number of cycles of oscillation per second is defined as the frequency, *f*, of the field and is expressed in hertz (Hz). In the spatial domain, the distance between two peaks of one oscillation cycle is called the wavelength. In free space, this is equivalent to:

$$\lambda = \frac{c}{f}$$

where:

c is the velocity of light (≈ 3.10^8 m/s).

Magnetic-field strength (H): The magnitude of a field vector in a point that results in a force (F) on a charge q moving with the velocity v:

$$F = q \ (\mathrm{v} \times \mu \mathrm{H})$$

The magnetic-field strength is expressed in units of ampere per metre (A/m).

Magnetic-flux density (B): The magnitude of a field vector that is equal to the magnetic field strength H multiplied by the permeability (μ) of the medium:

$$B = \mu \, \mathrm{H}$$

Magnetic-flux density is expressed in units of tesla (T).

Mobile phone: (cell phone, hand-held phone) Electronic device used to make and receive phone calls across a wide geographical area allowing the user to be mobile. A mobile phone is connected to a cellular network provided by a mobile-network operator.

Modulation: The process, or result of the process, whereby some characteristic of one wave is varied in accordance with another wave or signal. There are three canonical modulation types:

- AM (amplitude modulation): information is imparted to an electromagnetic wave by varying its amplitude
- FM (frequency modulation): information is imparted to an electromagnetic wave by varying its frequency
- ϕM (phase modulation): information is imparted to an electromagnetic wave by varying its phase

FM and ϕM are actually closely related to each other, e.g. both can be expressed mathematically in terms of a phase modulation.

Multiple access, or channel multiple access: Multiple-access methods are required to allow multiple devices to operate simultaneously. The following multiple-access methods are available for transmitting a set of individual data streams:

- FDMA: frequency-division multiple access splits the communication spectrum into different frequency domain bands that are assigned to the different data streams.
- TDMA: time-division multiple access splits the communication spectrum into periodically repetitive time slots, each terminal or data stream has a fixed periodic time slot during which data may be transmitted.
- CDMA: code-division multiple access allows multiple transmitters to send data simultaneously, theoretically, in the same frequency and time-domain channels. Communication channels are separated in the code domain by multiplying (spreading) the data streams with mutually orthogonal code vectors. Applying the same code vectors at the receiver allows separation of multiple simultaneous data streams due to the orthogonality of the codes.
- SDMA: space-division multiple access separates different data streams in space. A prominent example is directional radio systems.

In principle, the same multiple-access methods can be used to divide the forward and return data stream between two terminals. In practice however only time-division duplex (TDD) and frequency-division duplex (FDD) are applied.

Peak spatial SAR (psSAR): Peak spatial SAR values describe the peak SAR of all sSAR (See specific absorption rate [SAR] and spatially averaged SAR [sSAR]).

Peak-to-average power ratio (PAPR): The probability of peak signal power exceeding the average power level by 0.1%. In the case of non-statistical disruptions, PAPR is equivalent to the crest factor, i.e. 2 for a sinusoidal signal, 8.7 for GSM, 3.1–3.3 for UMTS-FDD, 10–20 for WLAN, etc. In the case of pulsed signals, the peak pulse amplitude is PAPR multiplied by the average power.

Penetration depth: For a plane electromagnetic wave incident on the boundary of a medium, the distance from the boundary into the medium along the direction of propagation in the medium, at which the field strengths of the wave have been reduced to 1/e (around 37%) of their boundary values. Penetration depth is expressed in metres (m).

Permittivity: The ratio of the electric-flux density in a medium to the electric-field strength at a point. The permittivity of biological tissues is dependent on frequency. Permittivity is expressed in units of farad per metre (F/m).

Polarization: The property of a radiated electromagnetic wave describing the time-varying direction and amplitude of the electric-field vector; specifically, the figure traced as a function of time by the extremity of the E-field vector at a fixed location in space, as observed along the direction of propagation.

Power density (Pd): The radiant power incident perpendicular to a surface, divided by the area of the surface. The power density is expressed in units of watt per square metre (W/m^2). Power density can be determined from the field strengths as follows:

$$P_d = E \times H = \frac{E^2}{377\Omega} = 377\Omega\ H^2$$

Also written as:

$$P_d = E \times H = E^2|377\Omega = 377\Omega\ H^2$$

Radiation: The emission and propagation of energy in the form of waves or particles through space.

Radiofrequency: Any frequency in the range of 30 MHz to 300 GHz.

Receiver: A device that detects radio signals and extracts useful information that has been encoded onto them through modulation, such as speech, music, data or pictures.

Resonance: The tendency of an object to oscillate with a larger amplitude at certain frequencies.

Root-mean-square (rms): The rms value or effective value is the square root of the mean of the squares of a continuous function:

$$f_{rms} = \sqrt{\frac{1}{T_2 - T_1} \int_{T_1}^{T_2} [f(t)]^2 dt}$$

where:
T is period
t is time
f is frequency
The rms values are important in the context of expressing exposure values averaged over time (see also specific absorption rate, SAR).

Root-sum-square (rss): The rss value is the root of the sum of the squares of the components of a vector.

Sidelobes: Antennae designed to radiate a main beam in particular angular direction also produce weaker beams known as sidelobes in other angular directions.

Spatially averaged SAR (sSAR:): Spatially averaged SAR (sSAR) values have been defined to better characterize SAR with respect to potential hazards. Technically, each location of the body is represented with a spatially averaged SAR. Different definitions have been proposed for standard settings and are commonly applied:

- **sSAR-1 g**: spatially averaged SAR values over a mass of 1 g of tissue in the shape of a cube. Special evaluation conditions are applied in case of air interfaces (IEEE C95.3). In practice, each local SAR value in the body is represented by the sSAR-1 g value whereby the cube is grown symmetrically around that location. At higher frequencies, sSAR-1 g is approximately twice the value of sSAR-10 g due to the reduced penetration depth.
- **sSAR-10 g**: spatially averaged SAR values over a mass of 10 g of tissue in the shape of a cube.
- **sSAR-10 g c**: spatially averaged SAR values over a mass of 10 g of contiguous tissue.

Specific absorption rate (SAR): The time derivative of the incremental energy (dW) absorbed by (dissipated in) an incremental mass (dm) contained in a volume element (dV) of given density (ρ):

$$SAR = \frac{d}{dt}\left(\frac{dW}{dm}\right) = \frac{d}{dt}\left(\frac{dW}{pdV}\right)$$

The SI unit of SAR is the watt per kilogram (W/kg).

NOTE: SAR can be related to the electric field at a point by:

$$SAR = \frac{\sigma |E|^2}{\rho}$$

where:
σ is conductivity of the tissue (S/m)
ρ is mass density of the tissue (kg/m^3)
E is rms electric field strength in tissue (V/m)
NOTE: SAR can be related to the increase in temperature at a point by:

$$SAR = \frac{c\Delta T}{\Delta t}\Big|_{t=0}$$

where:
ΔT is the change in temperature (°C)
Δt is the duration of exposure (s)
c is the specific heat capacity (J/kg °C)
This assumes that measurements are made under "ideal" non-thermodynamic circumstances, i.e. no heat loss by thermal diffusion, radiation, or thermoregulation (blood flow, sweating, etc.). Therefore, the third equation is only valid if the exposed body is in thermal equilibrium or a steady thermal state at the beginning of the exposure and either heat exchange processes can be neglected during the measurement interval or the processes are known and corrected such that dT can be correspondingly corrected.

In other words, SAR is proportional to the absorbed energy, square of the induced E-fields or induced current density. However, SAR is not directly proportional to the induced magnetic field.

Specific tissue-averaged SAR (stSAR): The total electromagnetic power absorbed by an organ or specific tissue.

Standing waves: Standing waves are formed where RF fields are contained by reflection back and forth. Energy is stored in the space where reflection occurs, which leads to high field strengths that are not associated with radiation. Fields associated with standing waves generally deposit much less energy in the body tissues than radiation fields of the same strength.

Time-averaged SAR or **temporal-averaged SAR:** SAR is usually reported as time-averaged SAR, either over the periodicity of the signal or over any 6 minutes.

Transceiver: A device containing both a transmitter and a receiver, such that it forms one terminal in a duplex communications link.

Transmitter: A device that generates and amplifies a carrier wave, modulates it to carry information, and radiates the resulting signal from an antenna, such that it can be received elsewhere.

UMTS (Universal Mobile Telecommunications System): a third-generation mobile telecommunications technology that uses digitally encoded signals to enable user access.

Whole-body SAR or **whole-body averaged SAR (wbSAR):** The whole-body SAR is the total electromagnetic power absorbed by a body divided by its mass.

Wi-Fi: a wireless transmission technique for use in local area networks that works in 2.4 GHz and 5 GHz bands. It is a registered trademark of the Wi-Fi Alliance.

WLAN (wireless local area network): a short-range wireless data communications network linking two or more devices.

WPAN (wireless personal area networks): a short-range wireless communications network for personal devices located near to the individual, e.g. Bluetooth.

LIST OF ABBREVIATIONS

AMPS	advanced mobile phone system
CMB	cosmic microwave background
CDMA	code-division multiple access
CW	continuous wave
DAB	digital audio broadcasting
D-AMPS	digital advanced mobile phone system
DECT	digital enhanced cordless telecommunications
DCS	digital cellular system
DMH	dimethylhydrazine
DTX	discontinuous transmission
EIRP	equivalent isotropically radiated power
EMF	electromagnetic field
ENU	*N*-ethyl-*N*-nitrosourea
ERP	effective radiated power
FDD	frequency-division duplex
FDMA	frequency-division multiple access
FDTD	finite-difference time-domain
FEM	finite-element method
GPRS	general packet radio service
GSH-Px	glutathione peroxidase
GSM	Global System for Mobile communications
HAN	home area network
HF	high frequency
ICNIRP	International Council on Non-Ionizing Radiation Protection
iDEN	integrated Digital Enhanced Network
IRP	spherically-integrated radiated power
ISM	industrial, scientific and medical
LAN	local area network
LF	low frequency
LPS	lipopolysaccharide
LTE	long-term evolution
MF	medium frequency
MoM	method of moment
MPE	maximum permissible exposures
MRI	magnetic resonance imaging

MX	3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone
NAC	*N*-acetyl cysteine
NO	nitric oxide
ODC	ornithine decarboxylase
OFDM	orthogonal frequency-division multiplexing
PCI	peripheral component interconnect
PDC	personal digital cellular
PHA	phytohaemagglutinin
PMA	phorbol 12-myristate 13-acetate
PMR	private mobile radio
PTT	push-to-talk
pps	pulses per second
PVC	polyvinyl chloride
PW	pulsed wave
MMC	mitomycin C
NMT	Nordic Mobile Telephony
RF	radiofrequency
ROS	reactive oxygen species
RTL	radial transmission line
RT-PCR	reverse-transcriptase polymerase chain reaction
SAM	specific anthropometric mannequin
SAR	specific absorption rate
SD	standard deviation
SMS	short message service
SOD	superoxide dismutase
TAC	total antioxidant capacity
TACS	total-access communication systems
TCSE	total cumulative specific energy
TDMA	time-division multiple access
TEM	transverse electromagnetic
TETRA	Terrestrial Trunked Radio
TNF	tumour necrosis factor
TPA	12-*O*-tetradecanoylphorbol-13-acetate
UMTS	Universal Mobile Telecommunications System
vs	*versus*
WCDMA	wideband code-division multiple access
Wi-Fi	standard wireless local area network (WLAN) technology
WiMax	worldwide interoperability for microwave access
WLAN	wireless local area network
XO	xanthine oxidase

CUMULATIVE CROSS INDEX TO *IARC MONOGRAPHS*

The volume and year of publication are given. References to corrigenda are given in parentheses.

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LIST OF *IARC MONOGRAPHS*

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1972; 184 pages (out-of-print)

Volume 2

Some Inorganic and Organometallic Compounds

1973; 181 pages (out-of-print)

Volume 3

Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds

1973; 271 pages (out-of-print)

Volume 4

Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents

1974; 286 pages (out-of-print)

Volume 5

Some Organochlorine Pesticides

1974; 241 pages (out-of-print)

Volume 6

Sex Hormones

1974; 243 pages (out-of-print)

Volume 7

Some Anti-Thyroid and Related Substances, Nitrofurans and Industrial Chemicals

1974; 326 pages (out-of-print)

Volume 8

Some Aromatic Azo Compounds

1975; 357 pages (out-of-print)

Volume 9

Some Aziridines, N-, S- and O-Mustards and Selenium

1975; 268 pages (out-of-print)

Volume 10

Some Naturally Occurring Substances

1976; 353 pages (out-of-print)

Volume 11

Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics

1976; 306 pages (out-of-print)

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Some Carbamates, Thio- carbamates and Carbazides

1976; 282 pages (out-of-print)

Volume 13

Some Miscellaneous Pharmaceutical Substances

1977; 255 pages

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1977; 106 pages (out-of-print)

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Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals

1977; 354 pages (out-of-print)

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Some Aromatic Amines and Related Nitro Compounds—Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals

1978; 400 pages

Volume 17

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1978; 365 pages

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Polychlorinated Biphenyls and Polybrominated Biphenyls

1978; 140 pages (out-of-print)

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Some Monomers, Plastics and Synthetic Elastomers, and Acrolein

1979; 513 pages (out-of-print)

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Some Halogenated Hydrocarbons

1979; 609 pages (out-of-print)

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1979; 583 pages

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Some Non-Nutritive Sweetening Agents

1980; 208 pages

Volume 23

Some Metals and Metallic Compounds

1980; 438 pages (out-of-print)

Volume 24

Some Pharmaceutical Drugs

1980; 337 pages

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Wood, Leather and Some Associated Industries

1981; 412 pages

Volume 26

Some Antineoplastic and Immunosuppressive Agents

1981; 411 pages (out-of-print)

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Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-water and Dental Preparations

1982; 341 pages (out-of-print)

Volume 28

The Rubber Industry

1982; 486 pages (out-of-print)

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Some Industrial Chemicals and Dyestuffs

1982; 416 pages (out-of-print)

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Miscellaneous Pesticides

1983; 424 pages (out-of-print)

Volume 31

Some Food Additives, Feed Additives and Naturally Occurring Substances

1983; 314 pages (out-of-print)

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Polynuclear Aromatic Compounds, Part 1: Chemical, Environmental and Experimental Data

1983; 477 pages (out-of-print)

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Polynuclear Aromatic Compounds, Part 2: Carbon Blacks, Mineral Oils and Some Nitroarenes

1984; 245 pages (out-of-print)

Volume 34

Polynuclear Aromatic Compounds, Part 3: Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production, and Iron and Steel Founding

1984; 219 pages (out-of-print)

Volume 35

Polynuclear Aromatic Compounds, Part 4: Bitumens, Coal-tars and Derived Products, Shale-oils and Soots

1985; 271 pages

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Allyl Compounds, Aldehydes, Epoxides and Peroxides

1985; 369 pages

Volume 37

Tobacco Habits Other than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines

1985; 291 pages (out-of-print)

Volume 38

Tobacco Smoking

1986; 421 pages

Volume 39

Some Chemicals Used in Plastics and Elastomers

1986; 403 pages (out-of-print)

Volume 40

Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation

1986; 444 pages (out-of-print)

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Silica and Some Silicates

1987; 289 pages

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Man-Made Mineral Fibres and Radon

1988; 300 pages (out-of-print)

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Alcohol Drinking

1988; 416 pages

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Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels

1989; 322 pages

Volume 46

Diesel and Gasoline Engine Exhausts and Some Nitroarenes

1989; 458 pages

Volume 47

Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting

1989; 535 pages (out-of-print)

Volume 48

Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry

1990; 345 pages

Volume 49

Chromium, Nickel and Welding

1990; 677 pages

Volume 50

Pharmaceutical Drugs

1990; 415 pages

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Coffee, Tea, Mate, Methylxanthines and Methylglyoxal

1991; 513 pages

Volume 52

Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds

1991; 544 pages

Volume 53

Occupational Exposures in Insecticide Application, and Some Pesticides

1991; 612 pages

Volume 54

Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals

1992; 336 pages

Volume 55

Solar and Ultraviolet Radiation

1992; 316 pages

Volume 56

Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins

1993; 599 pages

Volume 57

Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines

1993; 428 pages

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Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry

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Hepatitis Viruses

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Wood Dust and Formaldehyde

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Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals

1995; 551 pages

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Human Papillomaviruses

1995; 409 pages

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Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds

1996; 578 pages

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Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses

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Polychlorinated Dibenzo-para-Dioxins and Polychlorinated Dibenzofurans

1997; 666 pages

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Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8

1997; 524 pages

Volume 71

Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide

1999; 1586 pages

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Hormonal Contraception and Post-menopausal Hormonal Therapy

1999; 660 pages

Volume 73

Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances

1999; 674 pages

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Surgical Implants and Other Foreign Bodies

1999; 409 pages

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Ionizing Radiation, Part 1, X-Radiation and γ-Radiation, and Neutrons

2000; 492 pages

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2000; 522 pages

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2000; 563 pages

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2001; 595 pages

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2001; 763 pages

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Non-ionizing Radiation, Part 1: Static and Extremely Low-frequency (ELF) Electric and Magnetic Fields

2002; 429 pages

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Man-made Vitreous Fibres

2002; 418 pages

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Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene

2002; 590 pages

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Tobacco Smoke and Involuntary Smoking

2004; 1452 pages

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Some Drinking-Water Disinfectants and Contaminants, including Arsenic

2004; 512 pages

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Betel-quid and Areca-nut Chewing and Some Areca-nut-derived Nitrosamines

2004; 334 pages

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Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide

2006; 330 pages

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Inorganic and Organic Lead Compounds

2006; 506 pages

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Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol

2006; 478 pages

Volume 89

Smokeless Tobacco and Some Tobacco-specific N- Nitrosamines

2007; 626 pages

Volume 90

Human Papillomaviruses

2007; 670 pages

Volume 91

Combined Estrogen- Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy

2007; 528 pages

Volume 92

Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures

2010; 853 pages

Volume 93

Carbon Black, Titanium Dioxide, and Talc

2010; 452 pages

Volume 94

Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins

2010; 450 pages

Volume 95

Household Use of Solid Fuels and High-temperature Frying

2010; 430 pages

Volume 96

Alcohol Consumption

2010; 1431 pages

Volume 97

1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide)

2008; 510 pages

Volume 98

Painting, Firefighting, and Shiftwork

2010; 806 pages

Volume 99

Some Aromatic Amines, Organic Dyes, and Related Exposures

2010; 692 pages

Volume 100A

Pharmaceuticals

2012; 435 pages

Volume 100B

Biological Agents

2012; 475 pages

Volume 100C

Arsenic, Metals, Fibres, and Dusts

2012; 501 pages

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2012; 341 pages

Volume 100E

Personal Habits and Indoor Combustions

2012; 575 pages

Volume 100F

Chemical Agents and Related Occupations

2012; 599 pages

Volume 101

Some Chemicals Present in Industrial and consumer products, food and drinking-water

2013 (published online: 2012); 586 pages

Volume 102

Non-ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields

2013; 460 pages

Supplement No. 1

Chemicals and Industrial Processes Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 20)

1979; 71 pages (out-of-print)

Supplement No. 2

Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal

1980; 426 pages (out-of-print)
(updated as IARC Scientific Publications No. 83, 1986)

Supplement No. 3

Cross Index of Synonyms and Trade Names in Volumes 1 to 26 of the IARC Monographs

1982; 199 pages (out-of-print)

Supplement No. 4

Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29)

1982; 292 pages (out-of-print)

Supplement No. 5

Cross Index of Synonyms and Trade Names in Volumes 1 to 36 of the IARC Monographs

1985; 259 pages (out-of-print)

Supplement No. 6

Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42

1987; 729 pages (out-of-print)

Supplement No. 7

Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1–42

1987; 440 pages (out-of-print)

Supplement No. 8

Cross Index of Synonyms and Trade Names in Volumes 1 to 46 of the IARC Monographs

1990; 346 pages (out-of-print)

Design by Au-delà des mots

IARC MONOGRAPHS

This Volume of the *IARC Monographs* provides an evaluation of the carcinogenic hazards associated with exposure to electromagnetic radiation in the radiofrequency range (30 kHz to 300 GHz).

Human exposures to radiofrequency electromagnetic fields can occur from use of personal devices (e.g. mobile telephones, cordless phones, Bluetooth, and amateur radios), from occupational sources (e.g. high-frequency dielectric and induction heaters, high-powered pulsed radars), and from environmental sources (e.g. mobile-phone base stations, broadcast antennae, and medical applications). The general population receives the highest exposure from transmitters close to the body, including hand-held devices such as mobile telephones. Typical exposures to the brain from mobile-phone base stations and from television and radio stations are several orders of magnitude lower than those from second-generation GSM handsets, while 3G phones emit, on average, about 100 times less radiofrequency energy than GSM phones. Similarly, the average output power of Bluetooth wireless hands-free kits is estimated to be around 100 times less than that of mobile phones.

An *IARC Monographs* Working Group reviewed epidemiological evidence, cancer bioassays, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans from exposure to these electromagnetic fields. With *"limited evidence"* for carcinogenicity in humans based on an increased risk of glioma – a malignant brain tumour – among heavy users of mobile telephones, radiofrequency electromagnetic fields were classified as *"possibly carcinogenic to humans" (Group 2B)*.

Comune di Sestino

Provincia di Arezzo

DELIBERAZIONE DELLA GIUNTA MUNICIPALE – COPIA

Atto N. **035** del Registro Generale Comunale in data **29 MARZO 2024**

Oggetto:

Procedimenti di VIA statale PNIEC, Progetti di Parchi Eolici denominati "Poggio delle Campane", "Sestino" e "Energia Monte Petralta" ubicati nel Comune di Badia Tedalda (AR) e nel Comune di Sestino (AR), costituiti da aerogeneratori, con relative opere connesse ed infrastrutture nel Comune di Sestino.

L'anno **DUEMILAVENTIQUATTRO,** il giorno **VENTINOVE** del mese di **MARZO** alle ore **12:40,** nella sala delle adunanze del Comune di Sestino, convocata con appositi avvisi, previa l'osservanza di tutte le formalità prescritte dalla vigente Legge, si è riunita la Giunta Comunale.

All'appello nominale risultano:

DORI FRANCO	**IL SINDACO**	**P**
FABBRETTI DAVIDE	**IL VICE SINDACO**	**P**
DONATI LETIZIA	**ASSESSORE**	**P**

e dunque per totali presenti n**. 3** e assenti n. 0.

Partecipa all'adunanza il **VICE SEGRETARIO COMUNALE (Del. G.M. n. 20/2022), Dott.ssa BARTOLUCCI SILVIA,** che provvede alla redazione del presente verbale.

IL SINDACO, constatato che gli intervenuti sono in numero legale, dichiara aperta la riunione ed invita i convocati a deliberare sull'oggetto sopraindicato.

LA GIUNTA MUNICIPALE DI SESTINO

Visto il Decreto Legislativo 18 Agosto 2000, n. 267 – "TESTO UNICO DELLE LEGGI SULL'ORDINAMENTO DEGLI ENTI LOCALI".

Premesso che, in base al disposto normativo di cui all'art. 151, comma 4 e dell'art. 153 comma 5 del Decreto Legislativo 18 Agosto 2000, n. 267 "TESTO UNICO DELLE LEGGI SULL'ORDINAMENTO DEGLI ENTI LOCALI" il presente provvedimento, costituendosi come un mero atto di indirizzo, non necessita di parere / proposta da parte del competente Responsabile del Servizio.

LA GIUNTA MUNICIPALE DI SESTINO

Premesso che:

- sono pervenuti dal Ministero dell'Ambiente e della Sicurezza Energetica (MASE) per l'avvio di un procedimento di Valutazione di Impatto Ambientale (VIA) di competenza statale per progetti relativi alla Valutazione di Impatto Ambientale ai sensi del D.Lgs n. 152/02 per la realizzazione di Parchi Eolici denominati *"Poggio delle Campane", "Sestino"* e *"Energia Monte Petralta*" tutti insistenti nel territorio comunale di Sestino (AR);
- le opere principali dei progetti, costituiti da Impianti Eolici di potenza elettrica pari a circa 30 MW, rientrano nella tipologia di cui all'Allegato IV alla Parte Seconda del Dlgs. 152/2006, al punto 2, lett. d), denominata "impianti eolici per la produzione di energia elettrica sulla terraferma con potenza complessiva superiore a 1 MW", pertanto i procedimenti sono di competenza statale.

Preso atto, dagli elaborati dei progetti presentati presso il Ministero dell'Ambiente e della Sicurezza Energetica, che le dimensioni degli aerogeneratori sono di circa m 180/202 ed aventi tutti potenza complessiva circa o superiore a 30 MW.

Considerato che, per quanto riguarda l'impatto visivo dei tre Parchi Eolici sul territorio comunale di Sestino, la situazione è complessa in quanto analizzando gli elaborati di *Intervisibilità*, *Analisi visiva – impatto cumulativo* è evidente come da gran parte del territorio comunale risultino visibili la maggioranza degli aerogeneratori .

Considerato che, ai fini della valutazione di impatti cumulativi , sono da segnalare le istanze che sono state presentate anche nel territorio comunale confinante di Badia Tedalda le seguenti istanze di VIA relative ad impianti di produzione di energia elettrica da fonti rinnovabili:

- [ID: 9796] Parco eolico "*Poggio Tre Vescovi"* per la produzione di energia da fonte rinnovabile mediante l'installazione di n. 11 aerogeneratori in Alta Valmarecchia nel comune di Badia Tedalda (AR);

- [ID: 9773]PAUR-Impianto di produzione dell'energia elettrica da fonte eolica avente potenza in immissione pari a 54 Mw con relativo collegamento alla rete elettrica – impianto denominato *"Badia del Vento"* ubicato in Comune di Badia Tedalda (AR);

- PAUR *"Passo di Frassineto"*, costituito da n. 7 aerogeneratori ubicati nei comuni Pieve Santo Stefano, Badia Tedalda e Sansepolcro;

- Verifica di assoggettabilità a VIA per Progetto di installazione di n. 2 aerogeneratori da 1 MW in località Poggio dell'Aquila, nei Comuni Pieve Santo Stefano e Badia Tedalda;

- Autorizzazione Unica ex art. 12 D.Lgs. n. 386/2003 per n. 1 aerogeneratore da 1 MW in località Poggio dell'Aquila nel Comune di Badia Tedalda .

Preso atto che nei Comuni di Sestino e Badia Tedalda sono ad oggi esistenti i seguenti impianti:

- n. 3 pale eoliche (mini eolico) in corrispondenza di Poggio del Termine, due delle quali ricadenti in Comune di Badia Tedalda ed una in Comune di Sestino;
- n. 3 pale eoliche (mini eolico) in località Calgaglia, tutte in Comune di Sestino.

Preso atto che altra importante interferenza è costituita dal costruendo *"Metanodotto Foligno-Sestino DN 1200 DP 75 bar" e "Metanodotto Sestino-Minerbio DN 1200 DP 75 bar"*, in corso di realizzazione .

La Regione Toscana ha valutato che rispetto alle aree naturali protette, come definite dalla L. 394/1991 e ai siti della Rete Natura 2000, gli impatti derivanti dalla sua attuazione potrebbero interferire con i seguenti siti:

- ZSC IT5180008 "Sasso di Simone e Simoncello"
- ZSC IT5310003 "Monti Sasso Simone e Simoncello"
- ZPS IT5310026 "Monte Carpegna e Sasso Simone e Simoncello"
- ZPS IT5180010 "Alpe della Luna"
- ZSC-ZPS IT4090006 "Versanti occidentali del Monte Carpegna, Torrente Messa, Poggio di Miratoio".

Considerato che la tipologia di turbine da installare comporta la redazione di Road Survey, per individuare tutti gli elementi di potenziale interferenza con il transito dei mezzi di trasporto dei componenti delle turbine, per consentire il transito dei suddetti mezzi.

Quanto sopra premesso (per una comprensione piu' chiara e precisa della questione di cui trattasi), il Comune di Sestino è stato dunque chiamato, necessariamente, ad esprimere una propria valutazione sulla progettualità in oggetto, che in questa sede esula dall'aspetto puramente tecnico, analizzando altresi' elementi e caratteri antropologici e naturalistico-territoriali.

E' stato effettuato uno studio attento e concreto della progettualità in trattazione, analizzando una pluralità di aspetti, e ponendo sulla bilancia gli elementi positivi e quelli negativi.

Il Comune di Sestino ha voluto coinvolgere anche la popolazione, e chiari sono i documenti (che si allegano alla presente) e le sottoscrizioni nelle quali i nostri Cittadini hanno espresso un deciso parere contrario ai progetti dei Parchi Eolici.

E’ giusto osservare che i progetti dei Parchi Eolici in trattazione andrebbero a realizzarsi, materialmente, nelle cd. “aree interne” dell’Appennino, con un ambiente ancora incontaminato e splendidamente variegato per i suoi contenuti naturalistici. Si tratta di territori complessi, ove in questi ultimi anni, anche allo scopo di ridurre una costante tendenza allo spopolamento, sono stati fatti dei buoni investimenti, per favorire il turismo e la conservazione delle tradizioni culturali locali.

In particolare, per quanto riguarda il nostro Comune, i Parchi Eolici andrebbero ad essere collocati in un ambito caratterizzato da ricchezze naturalistico-culturali quali i “Sentieri di Francesco”, le ciclopiste, la sentieristica del CAI, il “Sentiero del Granduca” e altri “tesori”.

Non meno importante la possibile incidenza sulle attività produttive tipiche dei nostri territori, come gli allevamenti di Chianine, le zone tartufigene…. e non ultimi i diversi B&B, che sono sorti in questo ultimo periodo come nuovo elemento di attrazione per gli stranieri e per le famiglie che “fuggono” dalle città per cercare momenti di pace e di tranquillita’.

E chiaramente non puo’ essere dimenticato che il progetto eolico in questione andrebbe a svilupparsi, materialmente e “spiritualmente”, attorno alla Riserva Naturale del Sasso di Simone, dal confine valmarecchiese con Miratoio ai crinali del Seminico, per continuare sulle alture di Monteromano, Martigliano e al confine con il Parco Interregionale di Carpegna, con tutte le conseguenze che possono facilmente essere intuite, incidendo inevitabilmente sulla biodiversità tipica dell’area protetta .

Purtroppo…..ed è cosa piuttosto nota…. e importanti studi scientifici lo confermano, gli “insediamenti” di pale eoliche, che nel nostro caso avrebbero anche la caratteristica di essere “mega”, sconsigliano di vivere nelle loro vicinanze, trasformano la fauna, e spesso anche la flora, per cause di interconnessione tra microclima, vegetazione e suolo prativo.

Alcune delle nostre piu’ belle località frazionali, come Petrella, Case Barboni, Martigliano, Casale, San Donato, Monterone, Colcellalto sarebbero le prime a soffrire di un ambiente artefatto, anche rumoroso, e perciò invivibile.

Verrebbero colpite le attività di allevamento della RAZZA CHIANINA allo stato brado e semibrado, mentre i nuovi flussi turistici naturalistici, ad oggi faticosamente conquistati, ne risentirebbero immediatamente e la conseguenza sarebbe un nuovo definitivo spopolamento dei territori interessati.

D’altro canto non sara’ inutile segnalare che già molte associazioni, semplici Cittadini, “comitati” hanno voluto dare il loro contributo, relazionando pareri fortemente negativi nei confronti della progettualità eolica, e fra gli altri ricordiamo le osservazioni del Club Alpino Italiano, le osservazioni dell’Associazione Mountain Wilderness Italia, le osservazioni dell’Associazione Italia Nostra, le osservazioni del Comitato Appennino Sostenibile, le osservazioni dell’Associazione Altura e quelle del CAI GRUPPO REGIONALE TOSCANA.

Per tutte le motivazioni di cui sopra, e che questa Amministrazione Comunale intende ovviamente fare proprie, ad unanimità di voti, legalmente espressi:

La Giunta Municipale di Sestino

DELIBERA

DI ESPRIMERE PARERE NEGATIVO E CONTRARIO allo sviluppo realizzativo dei Progetti di Impianti Eolici denominati *"Poggio delle Campane", "Sestino"* e "*Energia Monte Petralta"* ubicati nel Comune di Sestino (AR), con relative opere connesse ed infrastrutture .

Di dare atto che il suddetto parere negativo è allargato ad eventuali future istanze di realizzazione di Parchi Eolici nel ns. territorio comunale.

Di dare atto che il presente provvedimento si costituisce come un atto di indirizzo della deliberante GIUNTA MUNICIPALE DEL COMUNE DI SESTINO, esulando ovviamente dagli obbligatori pareri tecnico-gestionali d'ufficio, che restano di competenza esclusiva e professionale del Ufficio Tecnico Comunale del Comune di Sestino.

Di dare atto che, costituendosi il presente provvedimento come un mero atto di indirizzo, viene omessa la proposta, e quindi il relativo parere del responsabile del servizio, ai sensi dell'art. 49, comma 1, del Decreto Legislativo 18 Agosto 2000 n° 267 - "TESTO UNICO DELLE LEGGI SULL'ORDINAMENTO DEGLI ENTI LOCALI" .

La Giunta Municipale di Sestino
con separata ed unanime votazione
DELIBERA
DI DICHIARARE il presente atto IMMEDIATAMENTE ESEGUIBILE ai sensi di legge.

SPAZIO NON UTILIZZABILE

SPAZIO NON UTILIZZABILE

Approvato e sottoscritto:

IL VICE SEGRETARIO COMUNALE — IL SINDACO

F.to Dott.ssa BARTOLUCCI SILVIA — **F.to** DORI FRANCO

E' copia conforme all'originale da servire per uso amministrativo.

IL VICE SEGRETARIO COMUNALE

Dalla Residenza Comunale, 29 MARZO 2024 — **Dott.ssa BARTOLUCCI SILVIA**

Il Messo Notificatore - Responsabile delle Pubblicazioni del Comune di Sestino, visti gli atti d'ufficio, ed in relazione al disposto del Decreto Legislativo 18 Agosto 2000, n. 267, "TESTO UNICO DELLE LEGGI SULL'ORDINAMENTO DEGLI ENTI LOCALI"

A T T E S T A

- Che la presente Deliberazione:

(V) registrata al Prot. Com. n. 0002001/2024 in data 08 APRILE 2024, è stata affissa all'Albo Pretorio Comunale il giorno 08 APRILE 2024 per rimanervi quindici giorni consecutivi, come prescritto dall'art. 124, comma 1, del Decreto Legislativo 18.08.2000, n. 267;

(V) è stata Comunicata in data 08 APRILE 2024 con lettera Prot. Com. n. 0002002/2024 del 08 APRILE 2024 , Sig.ri capigruppo consiliari ai sensi dell'art. 125, primo comma, del Decreto Legislativo 18.08.2000, n. 267 .

Il Messo Notificatore – Resp. Pubblicazioni del Comune di Sestino

Dalla Residenza Comunale, lì 08 APRILE 2024 — **I.D. Regi Fabio**

Il sottoscritto Segretario Comunale, visti gli atti d'ufficio, ed in relazione al disposto del Decreto Legislativo 18 Agosto 2000, n. 267, "TESTO UNICO DELLE LEGGI SULL'ORDINAMENTO DEGLI ENTI LOCALI"

A T T E S T A

- Che la presente Deliberazione:

( ) è stata trasmessa con lettera prot. n. _____ , in data _____, su richiesta dei Sig.ri consiglieri, per il controllo, ai sensi dell'art. 127, commi 1 e 2, del D.Lgs. 18.08.2000, n. 267, al Difensore Civico _____

( ) è stata adottata ai sensi del disposto di cui all'art. 42, comma 4, del D.Lgs. 18.08.2000, n. 267.

[ ] trasmessa al _____con lettera prot. n. _____ , in data _____

( ) è stata trasmessa con lettera prot. n. _____ , in data _____ , alla Prefettura in relazione al disposto dell'art. 135, comma 2, del T.U.E.L., approvato con D.Lgs. 18.08.2000, n. 267

( ) è stata trasmessa con lettera del _____prot. n. _____, al _____ a richiesta del Sig. Prefetto fatta con lettera del _____, prot. n. _____

( ) è stata trasmessa con lettera prot. n. _____ , in data a

- Che il _____ha dichiarato l'illegittimità della presente Deliberazione, richiedendo l'eliminazione dei vizi riscontrati con: ( ) DECISIONE ( ) _____ n. ____, del _____ (art. 127, c 2, D.Lgs. 18.08.2000, n..267).

- Che la presente Deliberazione è divenuta esecutiva il giorno 29 MARZO 2024

(X) perchè dichiarata immediatamente eseguibile (art. 134, comma 4, D.Lgs.18.08.2000, n. 267)

( ) decorsi 10 giorni dalla pubblicazione (art. 134, comma 3, D.Lgs.18.08.2000, n. 267)

( ) decorsi 15 giorni (art. 127, comma 2, D.Lgs.18.08.2000, n. 267) dalla ricezione dell'atto da parte del DIFENSORE CIVICO_____

( ) avendo il DIFENSORE CIVICO _____Comunicato di non aver riscontrato vizi di legittimità (art. 127, c. 2, D.Lgs.18.08.2000, n. 267)

( ) a seguito delle modifiche apportate su richiesta del DIFENSORE CIVICO_____

( ) perché confermata con il voto favorevole della maggioranza assoluta dei componenti il Consiglio Comunale (art. 127, c. 2, D.Lgs.18.08.2000, n. 267) con Deliberazione C.C. n. _____del _____

( ) "Salvo / con" ANNULLAMENTO / MODIFICHE _____ da parte _____

( ) DECISIONE **( )**_____ n. _____.

- Che la presente Deliberazione è stata affissa all'Albo Pretorio Comunale per quindici giorni consecutivi dal 08 APRILE 2024 al 23 APRILE 2024 (art. 124, c. 1, del Decreto Legislativo 18.08.2000, n. 267).

Dalla Residenza Comunale, lì

IL VICE SEGRETARIO COMUNALE

( ) Che la presente deliberazione è stata **( )** ANNULLATA **( )** REVOCATA **( )**_____ dal _____ con **( )** DELIBERA **( )**_____ n. _____ del _____

( ) Che la presente deliberazione è stata **( )** RATIFICATA **( )** MODIFICATA **( )**_____ dal _____ con **( )** DELIBERA **( )** _____ n. _____ del _____

Il Vice Segretario Comunale

Dalla Residenza Comunale, lì _____

E' copia conforme all'originale da servire per uso amministrativo.

Colcellalto di Sestino, 19 luglio 2023

Spett.le Ufficio,

la popolazione della Frazione di Colcellalto, le comunità limitrofe e numerosi cittadini interessati ESPRIMONO preoccupazione, sconcerto e contrarietà verso i due progetti di impianto eolico ("Poggio delle Campane" [https://va.mite.gov.it/it-IT/Oggetti/Info/9807] e "Sestino" [https://va.mite.gov.it/it-IT/Oggetti/Info/9782]) di recente pubblicazione.

La messa in opera dei progetti, come peraltro si evince dalla documentazione allegata agli stessi, determinerebbe la fine dell'interesse antropico, paesaggistico e naturalistico per questa vallata, l'aumento dell'inquinamento acustico e la perdita di valore di tutti gli immobili, specie di quelli di chi ha scelto di porre in questo luogo già svantaggiato la sede della propria famiglia. Per di più, il relativo elettrodotto diretto a Badia Tedalda andrebbe pericolosamente a tagliare in due il centro abitato di Colcellalto, a ridosso delle case, sollecitando serie considerazioni per quanto concerne il rapporto fra elettromagnetismo e insorgenza di patologie. Sulla base delle evidenze scientifiche fornite dalla Professoressa Brunella Del Re (Università di Bologna), si riportano di seguito e in allegato le monografie della IARC (*International Agency for Research on Cancer*) sui campi elettromagnetici a bassa frequenza (prima parte del 2002) e a radiofrequenza (seconda parte del 2011). In entrambi i casi, i campi elettromagnetici vengono classificati, sulla base di studi epidemiologici e sperimentali, come agenti di classe 2B cioè "possibly carcinogenic to humans".

Pertanto, si CHIEDE a questo ufficio di intraprendere con la massima urgenza e attenzione tutti i passi necessari per bloccare in ogni sede la messa in opera degli impianti e il transito dell'elettrodotto all'interno di Colcellalto, nel rispetto della salute pubblica e del patto di fiducia con la popolazione di questa comunità.

La medesima istanza viene contestualmente inviata a tutti gli enti territoriali e governativi coinvolti.

Restiamo in attesa di un vostro riscontro.

Cordiali saluti,

Il sottoscritto, Martino Donati a cui si associano, con manifesta richiesta di adesione e autorizzazione di rappresentanza, i seguenti cittadini:

Martino Donati

Mario Baroni
Carla Coleschi
Silvia Magiotti
Roberto Milaneschi
Pino Rosati
Francesca Olivas
Silvia Rosi
Filippo Lorini
Dina Regi
Dino Donati
Stefano Leonessi
Monica Menichelli
Assunta Montini
Andrea De Santi
Giulio Pannilunghi
Katia Piacesi
Francesco Angelini
Alberto Parri

Debora Contucci
Manuela Milli
Daniela Grifoni
Ombretta Rosati
Andrea Baroni
Marta Bidi
Matteo Baroni
Chiara Gori
Silvia Ocello
Filippo Baroni
Maria Luisa Guerrieri
Raffaella Venturini
Ezio Angelini
Serena Milaneschi
Matteo Guasti
Marco Renzi
Luisa Cerri

Tommaso La Rocca
Elisa Lorini
Marco Fantignoli
Carla Regi
Davide Pecorelli
Beatrice Angelini
Rita Regi
Massimo Pecorelli
Gianfranco Contucci
Silvana Missaglia
Annalisa Venturini
Maria Paola Pecorelli
Gabriele Contucci
Giorgio Parri
Maria Paola Battirossi
Mirco Regi
Federica Bianchi