SSI report

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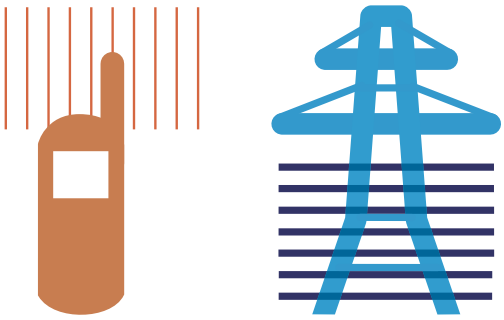
Recent Research on EMF and Health Risks

Fifth Annual Report from SSI:s Independent Expert Group on Electromagnetic fields, 2007

Revised edition 15 April, 2008



Statens strålskyddsinstitut
Swedish Radiation Protection Authority

SSI's Activity Symbols

Ultraviolet, solar and optical radiation
Ultraviolet radiation from the sun and solariums can result in both long-term and short-term effects. Other types of optical radiation, primarily from lasers, can also be hazardous. SSI provides guidance and information.

Solariums
The risk of tanning in a solarium are probably the same as tanning in natural sunlight. Therefore SSI's regulations also provide advice for people tanning in solariums.

Radon
The largest contribution to the total radiation dose to the Swedish population comes from indoor air. SSI works with risk assessments, measurement techniques and advises other authorities.

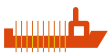
Health care
The second largest contribution to the total radiation dose to the Swedish population comes from health care. SSI is working to reduce the radiation dose to employees and patients through its regulations and its inspection activities.

Radiation in industry and research
According to the Radiation Protection Act, a licence is required to conduct activities involving ionising radiation. SSI promulgates regulations and checks compliance with these regulations, conducts inspections and investigations and can stop hazardous activities.

Nuclear power
SSI requires that nuclear power plants should have adequate radiation protection for the generalpublic, employees and the environment. SSI also checks compliance with these requirements on a continuous basis.

Waste
SSI works to ensure that all radioactive waste is managed in a manner that is safe from the standpoint of radiation protection.

Mobile telephony
Mobile telephones and base stations emit electromagnetic fields. SSI is monitoring developments and research in mobile telephony and associated health risks.



Transport
SSI is involved in work in Sweden and abroad to ensure the safe transportation of radioactive substances used in the health care sector, industrial radiation sources and spent nuclear fuel.

Environment
"A safe radiation environment" is one of the 15 environmental quality objectives that the Swedish parliament has decided must be met in order to achieve an ecologically sustainable development in society. SSI is responsible for ensuring that this objective is reached.

Biofuel
Biofuel from trees, which contains, for example from the Chernobyl accident, is an issue where SSI is currently conducting research and formulating regulations.

Cosmic radiation
Airline flight crews can be exposed to high levels of cosmic radiation. SSI participates in joint international projects to identify the occupational exposure within this job category.

Electromagnetic fields
SSI is working on the risks associated with electromagnetic fields and adopts countermeasures when risks are identified.

Emergency preparedness
SSI maintains a round-the-clock emergency response organisation to protect people and the environment from the consequences of nuclear accidents and other radiation-related accidents.

SSI Education
is charged with providing a wide range of education in the field of radiation protection. Its courses are financed by students' fees.

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TITLE / TITEL: Recent Research on EMF and Health Risks. Fifth Annual Report from SSI:sIndependent Expert Group on Electromagnetic fields, 2007

DEPARTMENT / AVDELNING: Department of Emergency Preparedness and Environmental Assessment / Avdelningen för beredskap och miljöövervakning

SUMMARY: The report for 2007 is divided into four different frequency fields: static fields, extremely low frequency fields (ELF), intermediate fields (IF) and radiofrequency fields (RF). Recent volunteer studies have shown that movement in very strong static magnetic fields (>1T, used in magnetic resonance imaging) can induce electrical fields in the body and sensations of vertigo in some people and also an impaired performance of a visual tracking task.

New data on ELF fields and childhood leukaemia published during the last year does not change the overall conclusions of the previous report. A review has concluded that it appears unlikely that ELF fields cause cardiovascular disease.

Only few experimental and epidemiological studies are available on health effects of IF electromagnetic fields.

One study reports that the whole body SAR is higher than previously thought when short subjects or children are exposed to far field RF waves as compared to tall subjects or adults. Recent, methodologically more rigorous human laboratory studies do not replicate the positive findings from smaller, less rigorous studies published a few years ago, but a few positive effects are reported. Few new data on mobile phone use and brain tumour risk have been published during the last year.

This years report also includes results from three surveys: The WHO Environmental Health Criteria (EHC) Document on ELF fields, The European Commission Scientific Committee on Newly Identified Health Risks (SCENIHR) has updated a previous opinion from 2001 regarding health risks from electric and magnetic fields and The UK Stakeholder Advisory Group on ELF EMF (SAGE).

SAMMANFATTNING: 2007 års rapport är uppdelad i fyra olika frekvensområden: statiska fält, lågfrekventa fält (ELF), intermediära fält (IF) och radiofrekventa fält (RF).Nyligen publicerade studier på frivilliga försökspersoner visar att rörelser i mycket starka statiska magnetiska fält (>1T vid användning av magnetkameror inom sjukvården) leder till induktion av elektriska fält i kroppen och även till yrsel hos en del exponerade och har också beskrivit effekter på synen.

De nya epidemiologiska resultat som publicerats under året om samband mellan ELF-exponering och barnleukemi påverkar inte våra tidigare slutsatser. En utvärdering av epidemiologiska studier visar att ett samband mellan hjärt-kärlsjukdomar och exponering för lågfrekventa magnetfält är osannolikt. Endast ett fåtal experimentella och epidemiologiska studier av hälsoeffekter från IF-fält finns tillgängliga.

En ny studie visar att helkroppsvärdet för SAR vid exponering på längre avstånd från RF-sändare kan vara högre för korta personer eller barn, jämfört med för långa personer eller vuxna. Nyare och bättre studier på frivilliga försökspersoner har som regel inte lyckats bekräfta de samband som setts i tidigare, mindre och inte så välgjorda, studier. Under det senaste året har det presenterats få nya data om ett eventuella samband mellan mobiltelefoni och hjärntumörrisk.

I rapporten kommenterar också rådet tre internationella utvärderingar som presenterades under 2007: WHO:s nyligen utgivna Environmental Health Criteria (EHC) Document on ELF Fields, EU-kommissionens vetenskapliga kommitté SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) som har uppdaterat ett tidigare utlåtande från 2001 om hälsorisker vid exponering för elektriska och magnetiska fält och UK Stakeholder Advisory Group on ELF EMF (SAGE) som behandlat försiktighetsåtgärder i samband med kraftledningar och elektriska installationer i bostäder

Statens strålskyddsinstitut
Swedish Radiation Protection Authority

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Preface

The Swedish radiation protection agency, SSI (Statens strålskyddsinstitut) has appointed an international independent expert group (IEG) for electromagnetic fields (EMF) and health. The task is to follow and evaluate the scientific development and to give advice to the SSI. With recent major scientific reviews as starting points the IEG in a series of annual reports consecutively discusses and assesses relevant new data and put these in the context of already available information. The result will be a gradually developing health risk assessment of exposure to EMF. The group began its work in the fall of 2002 and presented its first report in December 2003. This is the fifth annual report.

The composition of the group during 2007 has been:

Prof. Anders Ahlbom, Karolinska Institutet and Stockholm Center for Public Health, Stockholm, Sweden (chairman);

Prof. Jukka Juutilainen, University of Kuopio, Kuopio, Finland;

Dr. Bernard Veyret, University of Bordeaux, Pessac, France;

Prof. Harri Vainio, Finnish Institute of Occupational Health, Helsinki, Finland (formerly at IARC, Lyon, France);

Prof. Leeka Kheifets, UCLA, Los Angeles, USA (formerly at WHO, Geneva, Switzerland);

Prof. Anssi Auvinen, University of Tampere, Tampere and STUK - Radiation and

Nuclear Safety Authority, Finland;

Dr. Richard Saunders, Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards, Oxfordshire, UK

Scientific secretary:

Prof. Maria Feychting, Karolinska Institutet, Stockholm, Sweden.

Stockholm in December 2007

Anders Ahlbom

Chairman

Executive Summary

Static fields

Exposure to static magnetic fields much greater than the natural geomagnetic field is associated with industrial and scientific equipment that uses direct current, such as some welding equipment and various particle accelerators. However, the main source of exposure to large static magnetic fields (> 1 T) is in the use of magnetic resonance imaging for medical diagnostic purposes. Movement in such large static fields can induce electrical fields in the body and sensations of vertigo in some people; thresholds for which vary considerably within the population. Recent volunteer studies have confirmed these effects and have also reported the impaired performance of a visual tracking task after head movement within such large magnetic field.

ELF (extremely low frequency) fields

Cell studies

Several recent cell studies have found effects at exposure levels around 1 mT. These levels are 1000 times higher than the levels found in the general environment where fields are generally below 1 μT. The dose-response and mechanisms of these effects are not known and it is therefore not possible to draw conclusions about their relevance for exposures at environmental levels.

Animal studies

Two recent studies of the effects of relatively strong ELF magnetic fields on genotoxicity reported positive findings. Although previous animal studies have generally not seen similar effects, the new findings are not in direct conflict with prior studies because of differences in exposure levels, genotoxicity endpoints measured and other experimental variables. However, the new studies have some important limitations, and further studies are needed before conclusions can be drawn.

Epidemiological studies

New data on childhood leukaemia published during the last year does not change the overall conclusions of our previous report, but indicate that a follow-up of survival results may be worthwhile. A review of cardiovascular studies concluded that it appears unlikely ELF causes cardiovascular disease, which is consistent with the evaluation made by WHO Environmental Health Criteria Document on ELF Fields.

IF (intermediate frequency) fields

Only few experimental and epidemiological studies are available on health effects of IF electromagnetic fields. Additional studies would be important because human exposure to such fields is increasing due to new and emerging technologies, for example surveillance systems. Studies on possible effects associated with chronic exposure at low exposure levels are particularly relevant for confirming adequacy of current exposure limits.

RF (radiofrequency) fields

Dosimetry

An important dosimetry finding is that in the GHz range (mobile telephony) the whole body SAR is higher than previously thought when short subjects or children are exposed to far field waves as compared to tall subjects or adults. These data have been published by one group, and we await publications from other groups as well.

Cell studies

A large number of in vitro studies have been published recently investigating various outcomes, including effects on reactive oxygen species, genotoxicity, apoptosis, gene expression, immunology, and enzyme activity. Most of these studies have not demonstrated effects of RF exposure on the studied outcomes, including also attempts to replicate the genotoxic effects observed in the REFLEX European programme. Additional studies are currently underway, for example on gene expression, and some other areas need further investigation, such as effects on apoptosis in primary cell types.

Animal studies

Six recent studies on carcinogenicity, some with higher exposure levels than previously used, consistently report lack of carcinogenic effects, and two studies on genotoxicity report no increase in micronuclei or DNA strand breaks after RF exposure. These results are consistent with the majority of previous studies.

Human laboratory studies

Most recent volunteer studies have investigated the effects of GSM mobile phone RF radiation on cognitive function, sleep, heart rate variability, blood pressure, and hypersensitivity. In general, the recent, methodologically more rigorous studies do not replicate the positive findings from smaller, less rigorous studies published a few years ago, but a few positive effects are reported.

Epidemiological studies

Few new data on mobile phone use and brain tumour risk have been published during the last year. Two national Interphone publications are based on very small numbers and do not change the overall assessment, and two published meta-analyses provide little additional information. Validation studies indicate that there may be substantial recall errors in self-reported mobile phone use, which needs to be taken into consideration in the interpretation of studies, and studies on exposure assessment emphasize substantial variability in output power of mobile phones, which indicates heterogeneity in field strength in different usage circumstances. Recent studies of occupational exposures have generally been too small, or registry based with crude exposure assessment and lack of information on potential confounders. A study of RF exposure from military antennae has limitations that preclude conclusions about potential effects of environmental RF exposure.

Reviews

The recent WHO Environmental Health Criteria (EHC) Document on ELF Fields, downloadable from the WHO EMF Project website (www.who.int/emf) addresses the possible health effects of exposure to extremely low frequency (ELF) electric and mag-

netic fields. The advice from WHO stemming from this document is contained in a brief ELF Fact Sheet No. 322, available from the same web site.

ELF magnetic fields were classified as possibly carcinogenic to humans by IARC in 2002, a classification that essentially was based on epidemiological results for childhood leukaemia. The EHC document reviewed all recent epidemiologic, toxicologic and in vitro studies and re-affirmed this classification. The EHC document suggests that exposure limits be implemented in order to protect against established adverse acute effects of exposure to ELF fields. The uncertainties about the existence of chronic effects, i.e., childhood leukaemia, suggest that implementing low and no-cost precautionary procedures to reduce exposure is reasonable and warranted. However, these precautionary approaches should not compromise the obvious benefits brought by electric power.

The European Commission Scientific Committee on Newly Identified Health risks (SCENIHR) has updated a previous opinion from 2001 regarding health risks from electric and magnetic fields. The report is downloadable from the European Commission website.

For radio frequency fields the SCENIHR concludes that mobile phone use of less than 10 years does not pose risk of brain tumours. For long term use, data are sparse and conclusions are tentative. For diseases other than cancer, very little data are available. To date no epidemiological studies on children are available. Research has failed to provide consistent support for a relation with self-reported symptoms (electromagnetic hypersensitivity).

For intermediate frequency fields the SCENIHR concludes that data are very sparse. Proper health risk evaluation is, however, important because human exposure to such fields is increasing due to new and emerging technologies.

For ELF fields, the SCENIHR concludes that the previous assessment that ELF magnetic fields are possibly carcinogenic, based on childhood leukaemia results, is still valid.

For static fields, finally, adequate data for risk assessment are very sparse. New technologies, e.g., MRI machinery require that studies capable of providing data for risk assessment be performed.

Sammanfattning på svenska

Statiska fält

Exponering för mycket högre statiska magnetiska fält än det jordmagnetiska fältet förekommer i anslutning till industriella och vetenskapliga likströmsanläggningar, t ex vid svetsningsutrustning och partikelacceleratorer. Den huvudsakliga källan till exponering för starka statiska magnetiska fält (>1T) är dock användning av magnetkameror inom sjukvården. Rörelser i sådana fält leder till induktion av elektriska fält i kroppen och även till yrsel hos en del exponerade; tröskeln för detta varierar dock avsevärt inom befolkningen. Nyligen publicerade studier på frivilliga försökspersoner bekräftar dessa effekter och har också beskrivit effekter på synen efter huvudrörelser i starka statiska magnetfält.

ELF (extremt lågfrekventa) fält

Cellstudier

Ett flertal nypublicerade cellstudier har funnit effekter vid exponeringsnivåer omkring 1 mT. Dessa nivåer är omkring 1000 gånger högre än de exponeringsnivåer som förekommer i den allmänna miljön där fälten som regel är under 1 μT. Dos-responssambanden för dessa effekter liksom mekanismerna bakom dem är inte kända och det är därför inte möjligt att dra slutsatser om vilken relevans dessa resultat har för exponering på de nivåer som förekommer i den allmänna miljön.

Djurstudier

Två nya djurstudier av relativt starka ELF fält och genotoxicitet har funnit positiva resultat. Men även om tidigare studier som regel inte sett motsvarande effekter så är resultaten inte i direkt konflikt, på grund av olikheter i exponeringsnivåer, olika endpoints och andra försöksbetingelser. De nya studierna har dock viktiga begränsningar och ytterligare studier är nödvändiga innan slutsatser kan dras.

Epidemiologiska studier

De nya epidemiologiska resultat som publicerats under året påverkar inte våra tidigare slutsatser, men poängterar att en uppföljning av studierna av ett samband mellan ELF exponering och överlevnad vid leukemi är påkallad. En evaluering av forskningen om kardiovaskulär sjukdom och exponering för ELF fält kom till slutsatsen att det är osannolikt att ELF är en orsak till kardiovaskulär sjukdom, vilket är samma slutsats som WHO's Environmental Health Criteria utvärdering kom till.

RF (radiofrekventa) fält

Dosimetri

Ett nytt och viktigt forskningsresultat är att för GHz bandet (mobiltelefoni) så är helkropps SAR-värdet högre för korta personer eller barn, jämfört med för långa personer eller vuxna, när de exponeras för så kallade "far fields". Dessa resultat har ännu bara publicerats från en forskargrupp men vi förväntar oss ytterligare publikationer om detta.

Cellstudier

Ett stort antal in vitro studier som nyligen har publicerats har undersökt varierande utfall inklusive ”reactive oxygen species”, genotoxicitet, apoptos, genuttryck, immunologi och enzymaktivitet. De flesta av dessa studier har inte sett några effekter av RF exponering på de studerade utfallen; det gäller också upprepningarna av de genotoxiska försök som ingick i det europeiska så kallade REFLEX programmet. Ytterligare studier pågår, till exempel på genuttryck, och inom några områden, till exempel apoptos, krävs mer forskning.

Djurstudier

Sex nypublicerade studier av carcinogenicitet, några med högre exponering än i tidigare undersökningar, har inte funnit några effekter och två nya studier på genotoxicitet har inte funnit någon ökad förekomst av micronuclei eller DNA strand breaks i samband med RF exponering. Detta stämmer väl överens med huvuddelen av resultaten i tidigare publicerad forskning.

Frivilliga försökspersoner

De studier på försökspersoner som publicerats på senare tid har framför allt undersökt effekter från RF fält av den typ som används av GSM-tekniken. Det som studerats är kognitionsförmåga, sömn, hjärtfrekvensvariation, blodtryck och överkänslighet. I huvudsak har nyare och bättre studier inte lyckats bekräfta de samband som setts i tidigare, mindre och inte så välgjorda, studier, men i några fall har de nyare studierna sett samband mellan exponering och utfall.

Epidemiologiska studier

Det har bara presenterats lite nya data om ett eventuellt samband mellan mobiltelefoni och hjärntumörrisk under det senaste året. Två nationella studier från Interphoneprojektet har publicerats men de är baserade på mycket små tal och påverkar inte totalbedömningen; två metaanalyser som också publicerats är av tveksam kvalitet. Valideringsstudier visar att det förekommer betydande rapporteringsfel, vid självuppgiven information om mobiltelefonanvändning, som måste beaktas vid tolkning av resultat från epidemiologiska studier. Det finns några studier av yrkesexponering som publicerats under senare tid: de är dock antingen små eller baserade på grov registerinformation om exponering respektive confounding. En undersökning baserad på RF exponering från antenner använda inom det militära har sådana metodologiska begränsningar att inga slutsatser kan dras om eventuella effekter från den aktuella exponeringen.

Utvärderingar

WHO’s nyligen utgivna Environmental Health Criteria (EHC) Document on ELF Fields går igenom de möjliga hälsoriskerna från exponering för ELF elektriska och magnetiska fält (www.who.int/emf). De råd som emanerar ur detta dokument finns i en kortfattad ELF Fact Sheet No.322 som också finns på den angivna webbplatsen.

ELF magnetiska fält klassificerades år 2002 som ”possibly carcinogenic to humans” (2B) av IARC väsentligen utifrån epidemiologiska resultat rörande barnleukemi. EHC dokumentet granskade all nytillkommen forskning och kunde konstatera att den klassificeringen fortfarande gäller. I EHC dokumentet föreslår man att exponering för ELF fält ska begränsas så att akuta hälsoeffekter förhindras. I det osäkra kunskapsläget gällande kroniska hälsorisker (leukemi hos barn) anser man det rimligt att försiktighetsprincipen till-

lämpas och att exponeringen begränsas så länge det kan ske till låg, eller ingen, kostnad. Man skriver också att man därvid inte får äventyra de uppenbara fördelar som elanvändning för med sig.

EU-kommissionens vetenskapliga kommitté SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) har uppdaterat ett tidigare utlåtande från 2001 om hälsorisker vid exponering för elektriska och magnetiska fält. Denna rapport finns på kommissionens hemsida.

För radiofrekventa fält skriver SCENIHR att mobilanvändning under mindre än tio år inte är förenat med ökad risk för hjärntumör. För längre tids användning är det vetenskapliga underlaget tills vidare inte tillräckligt för annat än preliminära bedömningar. För andra sjukdomar än cancer är underlaget också otillräckligt. För barn och ungdomar finns idag inga data. När det gäller självrapporterade symtom har forskning inte kunnat visa några samband med RF fält från mobiltelefoni (elöverkänslighet).

För så kallade intermediära frekvenser konstaterar SCENIHR att det vetenskapliga underlaget är mycket begränsat. Välgrundade riskvärderingar är dock viktiga därför att exponeringen för denna typ av fält ökar till följd av användningen av ny och framväxande teknik.

För ELF fält instämmer SCENIHR i tidigare bedömningar om att exponeringen kan vara cancerframkallande hos människa, baserat på forskning om leukemi hos barn.

När det gäller statiska fält är det vetenskapliga underlaget för en riskvärdering mycket begränsat. Ny teknik, t ex magnetkameror, nödvändiggör studier som tar fram data för adekvat bedömning av risker.

Introduction

This year's report covers a broad range of topics and the whole EMF spectrum. While previous reports have been focused on particular subjects the current report is broader and is divided by frequency with sections on static fields, extremely low frequency fields (ELF), intermediate fields, and radiofrequency fields (RF). The reason is the very fast technological development. As a result, EMF are used in an increasing number of applications and the exposure pattern is changing quickly. MR machines of increasing strength are being used in hospitals and give rise to different types of EMF exposure, including static fields. Intermediate frequency exposure is used more and more commonly for example in surveillance systems, cashier machines etc and add to the exposure to EMF. Mobile technology is also changing quickly and wifi, blue tooth etc are used with increasing frequency which also changes the exposure pattern of the population.

Because of the rapid development of new technologies using static and intermediate frequency fields, proper risk assessment for those frequencies is important. Yet, such data are still sparse which makes evaluations uncertain. However, some potentially important data regarding exposure of relevance to MRI technology have recently been presented and are discussed in the current report.

Research results on ELF has been intriguing for a long time because epidemiological studies consistently found an association between ELF magnetic fields and childhood leukaemia incidence, while at the same time experimental research has been unable to identify a mechanism or even a plausible hypothesis about a mechanism. Some of the new results of animal and cellular studies are discussed in this report.

There has been a longstanding concern that children might be more sensitive to RF fields than adults but data to address this have not been and are still not available. However, some recent dosimetry results that appear to indicate that the size of the body affects the SAR value may be relevant. These results are discussed in the RF section.

Preamble

The Swedish Radiation Protection Authority, SSI (Statens strålskyddsinstitut) has appointed an international independent expert group (IEG) for electromagnetic fields (EMF) and health. The task is to follow and evaluate the scientific evidence, to summarize and interpret the results, and to give advice to the SSI. The overriding goal is to provide a continuously updated health risk assessment. The main activity is to produce an annual report in which recent scientific publications are evaluated and the results are put in overall context of previous research. In this preamble we explain the principles and methods that the IEG uses to achieve its goals.

Relevant research for EMF health risk assessment can be divided into broad sectors such as epidemiologic studies, experimental studies in humans, experimental studies in animals, and in vitro studies. Also studies on biophysical mechanisms, dosimetry, and exposure assessment are considered.

A health risk assessment evaluates the evidence within each of these sectors and then weighs together the evidence across the sectors to a combined assessment. This combined assessment should address the question of whether or not a hazard exists i.e., if there exists a causal relation between exposure and some adverse health effect. The answer to this

question is not necessarily a definitive yes or no, but may express the weight of the evidence for the existence of a hazard. If such a hazard is judged to be present, the risk assessment should also address the magnitude of the effect and the shape of the dose-response function, i.e., the magnitude of the risk for various exposure levels and exposure patterns. A full risk assessment also includes exposure characterization in the population and estimates of the impact of exposure on burden of disease.

Epidemiological and experimental studies are subject to similar treatment in the evaluation process. As a general rule, only articles that are published or accepted to be published, in English language peer-reviewed scientific journals are considered by the IEG. This does not imply that the IEG considers all published articles equally valid and relevant for health risk assessment. On the contrary, a main task of the IEG is to evaluate and assess these articles and the scientific weight that is to be given to each of them. The IEG examines all studies that are of potential relevance for its evaluations. However, in the first screening some of the studies are sorted out either because the scope is not relevant to the focus of a particular annual report, or because the scientific quality is insufficient to merit consideration. Such studies are normally not commented upon in the annual IEG reports. The IEG considers it to be of equal importance to evaluate positive and negative studies, i.e., studies indicating that EMF has an effect and studies not indicating the existence of such an effect. In the case of positive studies the evaluation focuses on alternatives to causation as explanation to the positive result: With what degree of certainty can one rule out the possibility that the observed positive result is produced by bias, e.g. confounding or selection bias, or chance. In the case of negative studies one assesses the certainty with which it can be ruled out that the lack of an observed effect is the result of (masking) bias, e.g., because of too small exposure contrasts or too crude exposure measurements; one also has to evaluate the possibility that the lack of an observed effect is the result of chance, a possibility that is a particular problem in small studies with low statistical power. Obviously, the presence or absence of statistical significance is only a minor factor in this evaluation. Rather, the evaluation considers a number of characteristics of the study. Some of these characteristics are rather general, such as study size, assessment of participation rate, level of exposure, and quality of exposure assessment. Particularly important aspects are the observed strength of association and the internal consistency of the results including aspects such as dose response relation. Other characteristics are specific to the study in question and may involve dosimetry, method for assessment of biological or health endpoint, the relevance of any experimental biological model used etc. For a further discussion of aspects of study quality, refer for example to the Preamble to the IARC (International Agency for Research on Cancer) Monograph Series [IARC 2002]. It is worth noting that the result of this process is not an assessment that a specific study is unequivocally negative or positive or whether it is accepted or rejected. Rather, the assessment will result in a weight that is given to the findings of a study.

The step that follows the evaluation of the individual studies within a sector of research is the assessment of the overall evidence from that sector with respect to a given outcome. This implies integrating the results from all relevant individual studies into a total assessment. This is based on the evaluations of the individual studies and takes into account, for each study, both the observed magnitude of the effect and the quality of the study. Note again, that for this process to be valid, all studies must be considered equally irrespective of their outcome. In the experience of the IEG, tabulation of studies with results and critical characteristics has proven to be a valuable tool.

In the final overall evaluation phase, the available evidence is integrated over various sectors of research. This phase involves combining the existing relevant pieces of evidence on a particular end-point from studies in humans, from animal models, in vitro studies, and from other relevant areas. The integration of the separate lines of evidence should take place as the last, overall evaluation stage, after the critical assessment of all (relevant) available studies for particular end-points. In the first phase, epidemiological studies should be critically evaluated for quality irrespective of the putative mechanisms of biological action of a given exposure. In the final integrative stage of evaluation, however, the plausibility of the observed or hypothetical mechanism(s) of action and the evidence for that mechanism(s) is a factor to be considered. The overall result of the integrative phase of evaluation, combining the degree of evidence from across epidemiology, animal studies, in vitro and other data depends on how much weight is given on each line of evidence from different categories. Human epidemiology is, by definition, an essential and primordial source of evidence since it deals with real-life exposures under realistic conditions in the species of interest. The epidemiological data are, therefore, given the greatest weight in the overall evaluation stage.

An example demonstrating some of the difficulties of making an overall evaluation is the evaluation of ELF magnetic fields and their possible causal association with childhood leukaemia. It is widely agreed that while epidemiology consistently demonstrates an association between ELF magnetic fields and increased occurrence of childhood leukaemia, the little support from observations in experimental models and the lack of support for plausible biophysical mechanisms of action leads to the overall evaluation of ELF magnetic fields, in IARC's terminology, as 'possibly carcinogenic to humans' (Group 2B).

Static fields

A health risk assessment of static magnetic fields has recently been carried out by WHO [WHO 2006] (see [IEGEMF 2006]). MRI equipment specifically has become a more recent focus of attention following the concerns about restrictions on staff exposure to the magnetic fields generated by such equipment, as reflected in the recently announced 4-year delay to the EU Physical Agents Directive (Directive 2004/40/EC) on minimum health and safety requirements for occupational exposure to physical agents, particularly EMF:

(http://ec.europa.eu/employment_social/emplweb/news/news_en.cfm?id=308)

Sources of exposure

Medical diagnosis using magnetic resonance imaging (MRI) systems, which at present is the main source of human exposure to large static magnetic fields, has expanded enormously during the last 30 years and there are currently many thousand systems worldwide [WHO 2006]. This expansion is partly due to its versatility as an imaging modality. MRI not only provides excellent detailed images of soft tissues but can also be used to provide functional images of blood flow, tissue perfusion or changes in blood oxygenation.

The static magnetic fields used by MRI systems are approximately 10,000 to 200,000 times the natural background geomagnetic field of 30-70 μT. Currently, the most widely used static magnetic field strength for clinical MRI is 1.5 T. MRI systems operating at 3.0 T appeared in the early 1990s and are becoming the systems of choice in centres dedicated to neuroimaging. More recently, interest has increased in the use of ultrahigh field

scanners and systems operating at 7 T – 9.4 T which have appeared at a few research sites. In Sweden, most hospitals have 1.5 T machines, and there are currently five 3 T machines in use. Small 7 T machines are used for animal experiments.

Other static magnetic field sources also associated with the use of direct current (DC) include the electrochemical industry, electrically powered transportation systems, welding and a variety of scientific applications. The latter include linear accelerators and synchrotrons, thermonuclear fusion equipment and nuclear magnetic resonance imaging and spectroscopy systems.

Interaction mechanisms

Static magnetic fields interact with moving charged particles, such as ions, leading to the induction of electric fields and currents (see above), and with magnetic field moments (dipoles) arising mostly from the orbital motion or spin of the electrons in an atom, which exert mechanical forces and torques on molecules and larger assemblages. Conventionally, interactions with charges comprise electrodynamic interactions, and those magnetic moments comprise magnetomechanical interactions. Both have been implicated in the sensations of vertigo and nausea that have been reported to occur, usually during head movement, in the strong static magnetic fields within and around some of the high-field MRI scanners.

Dosimetry

People exposed to the high static magnetic fields in MRI scanners comprise patients, who receive a benefit from the scan, and also medical and ancillary staff involved in patient care. In addition, staff involved in the construction of these machines, and technical maintenance staff can also be exposed. One particular issue that has been raised recently in connection with limits on occupational exposure to EMFs is the large electric fields and currents generated during bodily movement in the strong static magnetic field gradients found around the high field MRI systems.

The size of the electric field and therefore current induced in the body for a particular magnetic field and field gradient depends only on the velocity and direction of motion, relative to the field. Dosimetric calculation suggests that such induced electric fields will be substantial during normal movement around or within fields greater than 2–3 T, and may account for the numerous anecdotal reports of vertigo and nausea and occasionally magnetic phosphenes experienced by patients, volunteers and workers moving in the field.

Calculations performed for a body moving near and inside an MRI magnet [Crozier and Liu 2005; Liu, et al. 2003] have suggested that the induced fields and currents may in some circumstances exceed peripheral nerve stimulation thresholds, although such effects have not been reported. For example, Crozier and Liu calculate that a body moving at a constant speed of 0.5 m s^{-1} in a 4 T magnet, the maximum induced electric field strength is approximately 2 V m^{-1} [Crozier and Liu 2005]. However, these fields would be induced at the low frequencies (0.5 – 5 Hz) associated with head and body movement [Grossman, et al. 1988; MacDougall and Moore 2005] where nerve excitation thresholds are low.

Volunteer studies

Glover et al. investigated in some detail the theoretical and experimental basis for magnetic-field-induced vertigo experienced by people working in and around strong static magnetic fields [Glover, et al. 2007]. These authors reported that movement of 10 volunteers into the bore of a 7 T whole body magnet at a speed of 0.1 m s^{-1} resulted in a sensation of forward or backward rotation in two of the subjects. This direction of apparent rotation was reversed when the orientation of the subject was reversed in relation to the field, eg by moving from a supine to a prone position, suggesting an effect of induced current on the neural output of the vestibular system (organ of balance) of the inner ear. Such effect can be readily induced by passing an electric current directly through the head via electrodes which affect the firing rate of the afferent vestibular nerves; the brain interprets this as movement which contributes, for example, to the vestibulo-ocular reflex that controls eye movement [Fitzpatrick and Day 2004; Goldberg, et al. 1984].

In contrast to movement-induced effects, postural sway was significantly increased in about half of the subjects standing stationary adjacent to the MRI scanner in a field of ~ 0.8 T. The effect is thought to be consistent with differences in magnetic susceptibility between the calcite crystals that comprise the otoconia (otoliths) of the vestibular system and the surrounding fluid. Presumably, this effect, which does not result from time-dependent field changes, may also contribute to movement-induced vertigo by exerting a changing force on the otoliths as the subject moves into the bore of the magnet, which is interpreted as body movement.

It is clear that sensitivity to these effects varies considerably between individuals. Vertigo induced by other modalities such as motion has been attributed (eg [Golding 2006]) to discordant inputs from the vestibular system as well as those from visual and other senses, relaying conflicting information regarding the position and motion of the head and body. The wide variation in sensitivity between individuals is ascribed to differences in ability of individuals to resolve this conflict. Many individuals will habituate to repeated vertigo, and habituation programmes are considered the best counter measure to motion sickness in various occupational situations where vertigo is not uncommon [Golding 2006].

De Vocht et al. reported transient and variable effects on task performance in 27 subjects in close proximity to a 7 T MRI system which may be related to the above observations [de Vocht, et al. 2007]. Each subject performed a battery of cognitive tests at various distances from the bore of the magnet. The field strengths in each of three test locations were 1600 mT (high field), 800 mT (medium exposure) and 2 mT (negligible exposure). No switched gradient or RF magnetic fields were present. The subjects were required to make a standardized series of head movements in each exposure condition, generating rates of change of magnetic field of up to 0.3 T s^{-1} (at 1.6 T), before carrying out a battery of cognitive tests that included working memory tasks and tests of eye-hand coordination, visual perception, visuo-spatial processing, and visual tracking. These subjects were unaware of their exposure status. An additional battery of tests was carried out at the high field exposure condition where the subjects were asked to keep their heads stationary. De Vocht and colleagues describe an impairment of the performance of the visual tracking task, following standardised head movements at the three different locations, which increased with increasing magnetic field strength.

These results are consistent with previous reports of impairments in the performance of a visual tracking task near the bore of 1.5 and 3 T scanners [de Vocht, et al. 2006; de

Vocht, et al. 2003], although as the authors note the effects are weak and somewhat variable between studies. In addition, a decrement in eye-hand co-ordination of borderline statistical significance was also described in the present study. The authors conclude that visual sensory processing and eye-hand coordination may be affected by exposure to stray fields from MR scanners. These decrements in performance appear to depend on the rate of change of the magnetic field with time, and hence by implication on the magnitude of the electric field induced in the head. It would seem possible that the electric fields induced by head movement may interfere with the vestibulo-ocular reflex mechanisms, as described above, without interfering with cognitive processes directly. This possibility will only be resolved through further study.

Concluding remarks on static fields

Exposure to static magnetic fields much greater than the natural geomagnetic field is associated with industrial and scientific equipment that uses direct current, such as some welding equipment and various particle accelerators. However, the main source of human exposure to large static magnetic fields (> 1 T) is in the use of magnetic resonance imaging for medical diagnostic purposes. This technology is also used in certain surgical procedures and could lead to high occupational exposure to the medical personnel. Movement in such large static fields can induce electrical fields in the body and sensations of vertigo in some people; thresholds vary considerably within the population. Recent volunteer studies have confirmed these effects and have also reported the impaired performance of a visual tracking task after head movement within the magnetic field.

Extremely Low Frequency (ELF)

Cell studies

Most of the recent in vitro studies have been done at 50 Hz and with exposure levels around 1 mT. During the last year, the emphasis has been on genotoxic effects and gene expression.

Bernardini and co-workers studied the effects of exposure to 1 mT 50 Hz magnetic fields on heat shock proteins (HSP) in a model of primary culture of porcine aortic endothelial cells [Bernardini, et al. 2007]. Exposure induced an increase in the mRNA levels of Hsp27, Hsp70, Hsp90, which was statistically significant for Hsp70, but there was no effect on the HSP protein levels. A partial relocalization of Hsp27 in the nucleus was observed.

Several techniques were used by Jia and co-workers to investigate the effects of a 50 Hz 0.4 mT magnetic field on the clustering of purified epidermal growth factor receptors (EGFRs) in Chinese hamster lung cell membranes [Jia, et al. 2007]. Exposure lasted 30 min and led to EGFR clustering and further investigations showed that exposure interferes with the EGFR signalling pathway.

Some parameters of the differentiation of AtT20 D16V cells (pituitary corticotrope-derived) were studied by Lisi and co-workers under exposure to 50 Hz, 2 mT magnetic fields [Lisi, et al. 2006] in the presence of nerve growth factor (NGF) . These cells extend neurite-like processes and differentiate into neurosecretory-like cells. Under exposure, fluorescence microscopy showed an increase in intracellular calcium and decrease in pH.

In parallel, the exposed cells showed morphological changes in plasma membrane involving rearrangement in the distribution of actin filaments. This was interpreted as evidence that exposed cells were in an early stage of differentiation compared to sham-exposed cells.

Lupke et al. exposed human umbilical cord blood-derived monocytes for 45 min to 50 Hz 1 mT magnetic fields [Lupke, et al. 2006], and found a 50% increase in reactive oxygen species (ROS) release in agreement with their previous findings and comparable to that induced by lipopolysaccharide (cf. Review on ROS and ELF by Simko [Simko 2007]). Gene expression profiling using a whole human genome cDNA array showed alterations of 986 genes involved in metabolism, cellular physiological processes, signal transduction, and immune response. Real-time RT-PCR analysis of two of the significantly regulated genes indicated the regulation of cell activation via the alternative pathway, i.e. without inflammation and cytokine receptor involvement, whereas the delayed gene expression of the three other regulated genes suggested the suppression of inflammatory processes.

With the aim of detecting DNA damage in exposed cells, Mairs et al. used a sensitive method of analysing mutations in microsatellite sequences [Mairs, et al. 2007]. Exposure for 12 hours of UVW human glioma cells to magnetic fields alone (1 mT, 50Hz) led to a 3.75-fold increase in microsatellite mutations. In combined exposure with 0.3- and 3-Gy gamma irradiation, magnetic field exposure increased the mutagenic capacity by 2.6 and 2.75, respectively. The mutagenicity of exposure to ELF magnetic fields and that of combined exposure with ionizing radiation shown in this study needs independent confirmation and further studies on the consequences of alterations in microsatellite sequences before conclusion can be drawn on the mutagenic potential of ELF magnetic field exposure.

Genotoxicity and combined effects of ELF magnetic fields were also studied by Cho et al. [Cho, et al. 2007], who exposed CCD-986sk human fibroblasts to magnetic fields (0.8 mT, 60 Hz) alone or in combination with the radiomimetic agent bleomycin (BLM). The magnetic field was applied throughout the culture period, and the frequency of micronuclei (using the cytokinesis-block assay) and aneuploidy was analyzed at 28, 88 and 240 h after exposure to BLM. No effects were found from magnetic field exposure alone, but BLM-induced micronuclei and aneuploidy were significantly increased in the magnetic field exposed cells at all time points. The results are based on only two independently replicated experiments with 1000 cells examined in each experiment, but the results are internally consistent: the MF effects were observed in micronuclei and in aneuploidy of chromosomes 1 and 4.

Wahab et al. exposed human peripheral blood lymphocytes to 50 Hz magnetic fields for 72 hours (1 µT or 1 mT, square or sine waveform) [Wahab, et al. 2007]. The clastogenic potential of the field exposure was assessed by measuring the sister chromatid exchange (SCE) frequency. Weak, but significant increases in the number of SCE per cell was observed under some exposure conditions and square-wave signals seemed to have a stronger effect which can be interpreted as evidence of a role for induced currents in the samples as the induced currents are proportional to the frequency of the magnetic field.

The motility of spermatozoa was assessed by Iorio et al. under exposure to ELF magnetic fields at 50 Hz (square waveform at 5 and 2.5 mT, sine waveform at 5 mT) [Iorio, et al. 2007]. Only the square-wave field affected the motility of the spermatozoa and the in-

crease in motility lasted for 21 hours after the end of the 3-hour exposure. The harmonic content played a role in the elicitation of the effect as it did in the paper quoted above.

In the Czech Republic, yeast and bacteria were exposed for 24 min to strong magnetic fields (10 mT, 50 Hz), and 20% bacterial death was found in Paracoccus denitrificans bacteria [Fojt, et al. 2007]. This group had observed similar effects with bacteria E. coli, S. aureus and L. adecarboxylata and noticed that the amplitude of the effect depended on the shape of the bacteria (ca. 40% death in rod-like Gram-negative bacteria and ca. 20% in spherical Gram-positive bacteria). They also observed a slower growth of Saccharomyces cerevisae yeast under the same type of magnetic field exposure [Novak, et al. 2007]. However, the authors have no explanation for the shape-dependent effect which is expected for electric field across the membrane but not for magnetic fields.

Concluding remarks on ELF cell studies

Several recent cell studies have found effects at exposure levels around 1 mT. In some studies, fields with a square waveform seem more efficient in eliciting effects; one will need to test the hypothesis that this is due to induced currents that are more prominent when the frequency content of the signal is increased. The exposure levels where these recent studies have found effects are 1000 times higher than the levels found in the general environment where fields are generally below 1 μT. However, there are no experimental data about dose-response and no understanding of the biophysical mechanism, which could help predicting possible existence of a threshold. Therefore, the relevance of these recent findings for human exposures at environmental levels is not known at present.

Animal studies

Genotoxicity

Two recent studies have investigated genotoxic effects of relatively strong ELF magnetic fields. Both studies reported positive findings.

Udriou and co-workers [Udroiu, et al. 2006] sampled liver and peripheral blood from newborn mice (36-38 pups from four pregnant females per group) exposed to a 50 Hz, 650 μT magnetic field during the whole intra-uterine life (21 days), and bone marrow and peripheral blood from adult mice (15 per group) exposed to a similar magnetic field for the same period. Exposure to a 3-Gy dose of X-rays (5-6 animals per group) was used as positive control. The micronucleus test was performed with CREST antibody staining to differentiate between clastogenic and aneugenic effects. Micronuclei were counted in 2000 erythrocytes per animal. An increased frequency of micronuclei in both peripheral blood ($p<0.001$) and liver ($p<0.005$) was observed in newborn mice exposed to the magnetic field. Most of the induced micronuclei were CREST-negative, but in relative terms, the increase was four-fold in CREST-positive micronuclei (formed by a whole chromosome, i.e., indicating aneugenic effects) and two-fold in CREST-negative micronuclei (formed by a chromosome fragment, indicating clastogenic effects). The MF-induced changes were small compared to the often more than 20-fold increases caused by X-rays. No significant MF effects were found in adult mice. The authors concluded that there is a need of additional studies on the possible link between ELF magnetic fields and aneuploidy because of the importance of the latter in carcinogenesis. The study has some noteworthy limitations; in the analyses the 38 newborn mice are treated as independent

observations, although they came from 4 litters. Furthermore, the control group animals were apparently not sham-exposed.

Erdal and co-workers investigated genotoxic and cytotoxic potential of a 50 Hz, 1 mT magnetic field in Wistar rat tibial bone marrow cells [Erdal, et al. 2007]. Chromosomal aberrations, micronuclei, mitotic index, and the ratio of polychromatic erythrocytes (PCE; young, immature erythrocytes) to normochromatic erythrocytes (NCE; mature erythrocytes) were measured. Four female rats per group were exposed to a horizontal MF either for 4 h on one day or 4 h/day for 45 days. Mitomycin C (MMC, 2 mg/kg) was used as positive control and showed significant effects on all variables measured. There were no statistically significant differences in chromosomal aberrations between the MF exposed and control animals (although slightly higher aberration frequencies were found in the MF exposed groups). However, the mean number of micronucleus was significantly ($p<0.01$) increased in the rats exposed for 45 days. The size of this effect was about two-fold, compared to the 10-fold increase caused by MMC. The mitotic index and proportion of PCE were signficiantly decreased in the MF-exposed animals (after both 1-d and 45-d treatments), indicating cytotoxicity to bone marrow cells. Also these changes were smaller than those induced by MMC. The value of this study is limited by the low number of animals per group. The control animals were apparently not sham-exposed.

The majority of previous studies have not found evidence of genotoxicity of ELF magnetic fields, although some positive findings have been reported (for reviews, see [IARC 2002; WHO 2007; Vijayalaxmi and Obe 2005]. Positive results were found especially in studies that have combined ELF magnetic fields with known genotoxic agents [Juutilainen, et al. 2006]. However, most of the previous studies have been *in vitro* experiments and have used short exposure times compared to the two studies described above.

Previous animal studies reported no increase of micronuclei in erythrocytes of mice exposed to 50 Hz MFs for 72 h at 2 or 10 mT (Singh et al.1997) or for up to 90 days at 14 µT [Abramsson-Zetterberg and Grawe 2001; Svedenstal and Johanson 1998]. Lai and Singh reported significantly increased DNA strand breaks (measured by the Comet assay) in rat brain cells after exposure of the animals to a 60-Hz, 10-µT magnetic field for 24 or 48 h [Lai and Singh 2004]. The size of the effect was relatively small, but it was seen in several experiments. Exposure for 48 h caused a larger increase than exposure for 24 h. The same authors have previously reported similar effects after short (2 h) exposure to much higher magnetic flux densities of 0.1 to 0.25 mT [Lai and Singh 1997], but these findings could not be confirmed in similar experiments by McNamee et al. who exposed adult rats, adult mice and immature mice to 60 Hz magnetic fields at 0.1, 1 or 2 mT for 2 h [McNamee, et al. 2005].

Concluding remarks on ELF animal studies

Two recent studies of the effects of relatively strong (650 µT and 1 mT) ELF magnetic fields on genotoxicity reported positive findings. Although previous animal studies have generally not seen similar effects, the new findings are not in direct conflict with prior studies because of differences in exposure levels, exposure durations, genotoxicity endpoints and other experimental variables. The new studies have some important limitations, and independent replications are needed before conclusions can be drawn.

Recent epidemiology

Childhood Leukaemia

It has been hypothesized that night-time bedroom measurements may represent a more accurate reflection of a long-term exposure to extremely low-frequency magnetic fields or be a biologically more meaningful time-window, in the light of the melatonin hypothesis. To test this, a pooled analysis of studies on exposure to ELF-EMF and the risk of childhood leukaemia has been extended to examine night-time residential exposures [Schuz, et al. 2007]. Data from four countries (Canada, Germany, UK, US) that included residential measurements of at least 24 hours from which night-time ELF-EMF could be extracted was analyzed. The study included 1842 children with leukaemia and 3099 controls. The odds ratios for night-time ELF-EMF for exposure categories of 0.1-0.2 μT, 0.2-0.4 μT, and ≥ 0.4 μT compared to < 0.1 μT were 1.11 (95 percent confidence interval, 0.91, 1.36), 1.37 (0.99, 1.90) and 1.93 (1.11, 3.35). The results of the night-time exposure analysis differ only marginally from the previous pooled analysis. The fact that these estimates are similar to those derived using 24/48 hour geometric means (the odds ratios being 1.09, 1.20, and 1.98 respectively), indicates that the night-time component cannot, on its own, account for the pattern observed. The dose-response analysis, using either exposure measure, is primarily limited by the small number of children exposed to ELF-EMF of 0.4 μT or higher. The pattern of the data at these higher fields is compatible with trends ranging from a further increase in risk, to a constant risk or even a downward gradient. Thus this extended pooled analysis does not support the hypothesis that leukaemia risk in children is more strongly associated with residential measurements taken during the night-time due to exposure misclassification nor that exposure during the night is biologically more relevant.

In a novel approach, a study from Mexico assessed an effect of residential ELF exposure on acute leukaemia risk among genetically susceptible children, that is, those with Down syndrome [Mejia-Arangure, et al. 2007]. Mejia-Arangure and colleagues identified 42 acute leukaemia cases (34 ALL, 8 AML) with Down syndrome age 16 years or younger diagnosed in Mexico City between 1995 and 2003 and registered at special education schools and institutions in Mexico City. One hundred and twenty-four controls, who also had Down syndrome were recruited from specialized centres that did genetic karyotyping (2 of 5 centres from which cases arouse representing 56% of potential controls). Additionally, a hospital-based control group of 126 children was used to evaluate possible control selection bias. In-person interview of parents provided information on the child's medical history, the pregnancy, socioeconomic status, neighbourhood of Mexico City, family history of cancer, and exposure at home to herbicides, fertilizers, or insecticides. Traffic density was also determined for location of residence. Exposure to power-frequency MF blinded to case-control status, included 5 minute measurements at the front door and wire codes. The risk of acute leukaemia was elevated with exposure to a magnetic field equal to or greater than 0.6 microT, with an OR of 3.7 (1.05 - 13.06). For wire codes there was increased risk of acute leukaemia with both medium exposure (OR = 5.81) and high exposure (OR = 4.05). The idea to focus on children who are already at increased risk is good and has a potential to contribute new information. Additionally, the population seems to be exposed to relatively high fields increasing potential information value of the study. Unfortunately the only measurements available are those at front door. Also the sampling frame for both cases and controls is complicated and unclear. Although it is reported that all of the identified cases participated, it is unclear what the participation rates were among cases and controls, or how representative controls were in general.

Of note is markedly lower SES in cases than that of controls, which might reflect a biased sampling frame or differential participation of cases and controls, or perhaps the causal role of some aspects of low SES.

Last year we discussed the study by Foliart et.al., which was first to propose that magnetic fields above 0.3 μT might have an influence on the relapse and death from childhood leukaemia [Foliart, et al. 2006]. An additional analysis of this study reports no associations between magnetic field exposure and unfavourable tumour or clinical factors based on magnetic field exposures monitored shortly after diagnosis [Foliart, et al. 2007].

However, in an important first attempt at replication of the Foliart et.al., [2006], cases from the German childhood leukaemia study were followed to evaluate the survival rates among children exposed to different levels of the residential magnetic fields [Svendsen, et al. 2007]. The survival study included 595 cases who had had residential 24-h magnetic field measurements taken in the home where they lived for a year before diagnosis (96%) or longer (4%). The longest follow-up was 16.4 years and the median was 9.5 years. Compared to exposures below 0.1μT hazard ratios for exposures between 0.1 - 0.2 μT was 2.6 (1.3-5.2) based on 34 cases and 9 deaths, and for exposures above 0.2 μT, an HR = 1.6 (0.6-4.4) based on 18 cases with 4 deaths. The authors considered their results as generally consistent with Foliart et al results. However, the risk in the German study emerges at lower magnetic field levels and the study is based on small numbers. There are other important differences as well: Foliart excluded young children (as they have particularly poor survival and their disease is thought to be etiologically different). Additionally, in the Foliart study only children who were in remission were enrolled and followed up [Foliart, et al. 2006]. This study did not follow similar exclusions. Foliart made personal measurements in a prospective study. Here measurements were done in a bedroom of a child prior to diagnosis. First it is unclear in which house measurements were utilized here. Finally, event-free survival analysis was not available for this study. A joint analysis of a follow-up of other studies of childhood leukaemia for recurrence and survival might provide additional insights.

Cardiovascular disease

Kheifets and colleagues reviewed the epidemiologic evidence regarding the association of ELF EMF and cardiovascular disease [Kheifets, et al. 2007]. Of the eight large cohort studies with internal comparisons conducted in Canada, US, Denmark, Sweden and UK, half were based on job titles alone and the other four had at least some measurements available for exposure assessment. All but one had cardiovascular disease mortality as the end-point. Of the cohort studies, one showed a statistically significantly increased risk of myocardial infarction and another elevated mortality from cardiovascular disease for linemen. A key limitation was potential confounding, as no information on other risk factors was available. Two case-control studies with more information on lifestyle factors showed no effect of occupational ELF exposure. The review concluded that the evidence does not support an effect of ELF exposure on cardiovascular disease, which is consistent with the WHO EHC evaluation [WHO 2007]. It appears unlikely ELF causes cardiovascular disease and the topic is not a research priority.

Concluding remarks on ELF epidemiology

New data on childhood leukaemia published during the last year does not change the overall conclusions of our previous report, but indicate that a follow-up of survival results

may be worthwhile. A review of cardiovascular studies concluded that it appears unlikely that ELF causes cardiovascular disease, which is consistent with the evaluation made by WHO EHC.

Intermediate frequency (IF)

Intermediate frequency (IF) electromagnetic fields are here defined as the frequency range between extremely low frequency fields and radiofrequency fields. The generally used upper limit of ELF is 300 Hz, but varying definitions exist for the lower limit of RF. In WHO and ICNIRP publications on this topic [Litvak, et al. 2002; Matthes, et al. 1999], IF fields were defined as frequencies from 300 Hz to 10 MHz. Human exposure to IF fields is increasing due to new and emerging technologies. Examples of IF field sources are anti-theft devices at the exits of shops, induction heating cooking appliances in homes and industrial applications such as induction heaters and welding [SCENIHR 2007].

Current exposure guidelines in the IF range are based on extrapolation from known thresholds at lower frequencies (basically associated with electrical stimulation of cells) and higher frequencies (mainly associated with thermal effects). However, these hazard mechanisms apply only to acute exposures, and the extrapolation is based on possibly unjustified assumptions about frequency dependence of effects [Litvak, et al. 2002]. In addition to established mechanisms, well-founded and comprehensive risk assessment should consider also other information, such as well-conducted epidemiological and laboratory studies. In contrast to the active research on ELF and RF electromagnetic fields, only a very limited number of epidemiological and experimental studies have addressed the biological effects of IF fields [Glaser 1999; Hietanen 1999; Juutilainen and Eskelinen 1999; Leitgeb, et al. 2006; Litvak and Repacholi 1999; SCENIHR 2007]. While there is limited evidence for developmental effects [Huuskonen, et al. 1998; Juutilainen 2005], studies on other effects (such as carcinogenicity, genotoxicity, nervous system effects and general toxicity) are almost totally lacking.

Recent IF studies

Miyakoshi and co-workers investigated possible genotoxic effects of magnetic fields similar to those emitted by induction heating cook tops used in homes [Miyakoshi, et al. 2007]. Bacteria or cultured mammalian cells were exposed for 2 h to 23 kHz magnetic fields at 532 μT. The assays included bacterial mutagenicity (Ames test) in three commonly used strains of S. typhimurium (TA98, TA100, TA 1537) and two strains of E. coli (WP2 uvrA, WP2 uvrA pKM101), cytokinesis-block micronucleus assay in Chinese hamster CHO-K1 cells, DNA strand breaks (alkaline and neutral Comet assays) in CHO-K1 cells, HPRT gene mutations in Chinese hamster V-79 cells, and cell proliferation in CHO-K1 cells. Positive controls (genotoxic chemical agents) were used and induced clear responses in all experiments. No statistically significant IF magnetic field effects were observed in any of the assays, and the authors concluded that exposure to an IF magnetic field does not cause genotoxicity in bacteria or Chinese hamster cells. However, the number of independent repeats was low (n=3 or “at least three” in some cases) in all assays, so the study had very limited statistical power to detect weak effects (no calculations of statistical power were presented by the authors).

Lee et al. evaluated possible tumourigenic effects of a 20 kHz magnetic field with triangular waveform and flux density of 6.25 μT [Lee, et al. 2007]. The exposure characteris-

tics were chosen to simulate emissions of video display units and to correspond to the Korean exposure limit for the public. The experimental design included animal groups exposed to IF magnetic field alone and combined exposures to IF magnetic field and known chemical carcinogens in three different experimental models that tested IF fields as a possible promoter of mammary, lung and skin tumours. Mammary tumours were produced in female Sprague–Dawley rats by dimethylbenz(a)anthracene (DMBA), lung tumours in ICR mice by benzo(a)pyrene (BP), and skin tumours in female ICR mice by of DMBA and tetradecanoylphorbolester (TPA). The IF field exposure was 8 h/day for 14 weeks in the mammary tumour experiment, for 6 weeks in the lung tumour experiment, and for 20 weeks in the skin tumour experiment. No tumours were found in any of the assays in the groups exposed to the IF field alone, and IF field exposure did not increase the incidence of mammary, lung or skin tumours induced by the chemical treatments. Use of several different assays is a strength of this study. The main weakness is that only 20 animals per group were used (normal practice in carcinogenesis studies is at least 50 animals per group), which results in low statistical power to detect any differences.

Concluding remarks on IF fields

Only few experimental and epidemiological studies are available on health effects of IF electromagnetic fields. Additional studies would be important because human exposure to such fields is increasing due to new and emerging technologies. Studies on possible effects associated with chronic exposure at low exposure levels (below exposure limits) are particularly relevant for confirming adequacy of current exposure limits.

Radiofrequency (RF)

Dosimetry

Specific absorption rate (SAR) is determined under various exposure conditions using numerical models. Recent research has indicated that whole body SAR values are influenced by the size of the exposed person. The main finding is that in the GHz range (mobile telephony) the whole body SAR is substantially higher than the basic restriction when short subjects or children are exposed to far field waves at the reference level (e.g. 4.5 W/m^2 at 900 MHz). So far only a Japanese group [Hirata, et al. 2007; Wang, et al. 2006a] has published these data. Other groups have confirmed these findings and have reported results at conferences, but have not yet published their data. These findings cannot be taken for granted until these further studies have been published.

Similar data for exposure of the foetus are not yet available.

Exposure systems

In the RF range, a major effort has been done in the last years to achieve sufficient quality in exposure of animals and cells. The criteria were uniform SAR distribution in the target, or at least knowledge of SAR in various organs in the case of animal models, and good temperature control in case of cultured cells. Collaboration between physicists, engineers, and biologists has been most fruitful. However, there are still reports of experimental work without adequate description of the exposure system used or failure to characterize the system in terms of SAR distribution and resulting temperature elevation. In the worst

case, mobile telephones are used as an RF source, which makes it totally impossible to get a well-defined dosimetry.

One of the recent exposure systems developed for rodents has been the Ferris-wheel, which consists of horizontal "tubes" in which the animals are placed along the circumference of a wheel. The RF source is positioned at the centre of the wheel (parallel plates) and the outer edge of the wheel is either reflective or absorbing depending on the design. These systems have been used in major recent programmes on animal models of cancer and have been well characterized [Faraone, et al. 2006; Kuster, et al. 2006]. The advantages of these systems are good knowledge of organ SAR and relative uniformity of the fields inside the animals. The disadvantage lies in the fact that the animals are constrained and the associated stress may induce biological effects. Additionally, animals can be exposed only for a limited duration each day.

The trend is now to move to systems which allow for long-term exposure of "free-running" animals such as the reverberation chambers. Few results have been obtained yet using these chambers, e.g, on plants by the Ledoigt group in France [Roux, et al. 2006; Vian, et al. 2006] or mice in Korea [Huang, et al. 2005]. A major project using reverberation chambers is planned in the USA using mobile telephony signals on mice and rats (NIEHS).

In view of the focus on neural network and their possible role in detecting the RF energy, systems have been designed to allow for exposure of cultured neurons or brain slices placed above monitoring electrodes (e.g., [Koester, et al. 2007])

New exposure setups are being designed for near-field exposure of humans and animals, mimicking body-mounted antennas (e.g. [Koester, et al. 2007].

In conclusion, following the major improvements achieved in the recent years in quality of exposure systems, the trend is now to:

- Use systems that allow for uniform exposure of free-running animals,
- Mimic the new RF sources that are coming into use in mobile communications,
- Assess the uncertainty in dosimetric measurements and calculations (e.g., [Kuster, et al. 2006] which is a major challenge that spans beyond the design of exposure systems, into exposure assessment.

Cell studies

RF in vitro studies are still numerous in view of the low cost and short duration of these investigations and the trend to search for biomarkers of the effects of exposure.

Isolated neurons

Direct exposure of neurons had been done several times in the past but is becoming more informative thanks to the development of new culture types, electrophysiological techniques, and exposure systems.

In Italy, Platano et al. investigated the effects of RF acute exposure on ion channel currents in primary rat cortical neurons. CW and GSM signals were used at 900 MHz (2 W/kg, 90-s duration) [Platano, et al. 2007]. The current through voltage-gated calcium channels was measured using the patch-clamp technique. No difference was observed

under exposure in terms of current amplitude or current-voltage relationship in the channels.

Reactive oxygen species (ROS)

Human umbilical cord blood-derived monocytes and lymphocytes were exposed by Lantow et al. to CW or GSM signals (DTX and Talk modes) at 2 W/kg (30 or 45 min, continuous or intermittent 5 min ON/5 min OFF [Lantow, et al. 2006a]. TPA[1] treatment induced a significant increase in ROS production but RF exposure did not, whatever conditions were used.

The same group [Lantow, et al. 2006b] again assessed the production of ROS in human blood cells using various GSM signals at 0.5, 1.0, 1.5, and 2.0 W/kg. Heat shock and TPA induced a significant increase in ROS production in Mono Mac 6 cells but RF did not, and in combination with TPA and LPS[2], there was no further increase in ROS concentration under exposure.

As part of the European CEMFEC programme, Zeni et al. investigated the induction of ROS in murine L929 fibrosarcoma cells exposed to RF at 900 MHz, with or without co-exposure to the mutagen MX[3] [Zeni, et al. 2007]. Under either CW or GSM exposure (10 or 30 min; 0.3 and 1 W/kg), there was no increase in ROS concentration either with RF alone or in combination with MX.

While it has been suggested that RF exposure elicits ROS production in cells, there is today very little evidence of such a process occurring.

Genotoxicity

An attempt to replicate some of the positive findings of the REFLEX European programme was made by Speit and co-workers [Speit, et al. 2007] using the same cells, the same equipment and the same exposure conditions as Diem et al., i.e., 1800 MHz; 2W/kg, CW with intermittent exposure [Diem, et al. 2005]. ES1 human fibroblasts were exposed and the alkaline comet assay and the micronucleus test performed. The number of comets or micronuclei was not increased under exposure. The replication also failed when using the sensitive Chinese hamster cell line V79.

The discrepancies related to genotoxic effects of RF exposure are not fully resolved today, but several replication attempts of the few positive data have failed.

Apoptosis

In a study by Merola and colleagues the hypothesis was tested that a GSM 900 exposure (1 W/kg, for 24, 48, and 72 hours) could elicit alterations in proliferation, differentiation, and apoptosis in a neuroblastoma cell line [Merola, et al. 2006]. Exposure up to 72 h did not induce significant alterations of these three cell parameters.

Neuronal apoptosis was investigated by Joubert and co-workers in the human neuroblastoma cell line SH-SY5Y [Joubert, et al. 2006]. CW or GSM-900 signals were used at 2 W/kg for CW and 0.25 W/kg for GSM (24 hours in a wire-patch cell). CW exposure

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[1] 12-O-tetra-decanoylphorbol-13 acetate

[2] lipopolysaccharide

[3] 3-chloro-4-(dichloromethyl)-5-hy-droxy-2(5H)-furanone

caused a 2°C increase and thus the corresponding sham-exposed cells were exposed at 39°C. Apoptosis rate was assessed, immediately or 24 h after exposure, using three complementary methods. In all cases no effect on apoptosis was observed. The same group [Joubert, et al. 2007] exposed primary cultured neurons from cortices of embryonic Wistar rats to the same GSM signal at 900 MHz, 0.25 W/kg, and again did not observe any increase in apoptosis rate.

Overall, data on cellular apoptosis do not suggest any effects of RF exposure. However, there is a need to test other primary cell types to confirm the lack of effects of low-level RF exposure in non-tumoural cells.

Gene expression

The expression of 22,000 genes in a human glioblastoma-derived cell-line (U87MG) was monitored by Qutob and colleagues [Qutob, et al. 2006], 6 hours after a 4-hour exposure at 1.9 GHz (pulse-modulation, 0.1, 1.0, and 10.0 W/kg). Such exposure did not affect global gene expression.

In a follow-up study, the same group [Chauhan, et al. 2007b] assessed the effects of a similar exposure on the expression of late onset genes in the same U87MG cells after 24 hours of RF exposure. A monocyte-derived cell-line (Mono-Mac-6) was also exposed to the same fields but with an intermittent regimen. There was no alteration in either cell type under any of the exposure protocols, while heat shock used as a positive control caused changes in specific proteins in both studies.

As part of the REFLEX Project (European 5th Framework programme), six human cell types, both immortalized cell lines and primary cells, were exposed to 900 and 1800 MHz in various collaborative laboratories and labelled for transcriptome analysis using whole-genome cDNA arrays in one of the laboratories [Remondini, et al. 2006]. There was no change in gene expression in NB6 neuroblastoma cells, T lymphocytes, and CHME5 microglial cells. Between 12 and 34 up- or down-regulated genes were found in EA.hy926 endothelial cells, U937 lymphoblastoma cells, and HL-60 leukaemia cells.

Gene expression was studied in response to mobile phone radiation (GSM 900, 2.8 W/kg) in two variants of a human endothelial cell line: EA.hy926 and EA.hy926v1 [Nylund and Leszczynski 2006]. Gene and protein expression were altered in both cell lines but differently in each of the cell lines. The authors interpreted this as evidence that could explain, at least in part, the origin of discrepancies in replication studies between different laboratories.

Ennamany and colleagues found changes in the expression of stress genes in cells that were extracted from human reconstructed epidermis exposed to GSM 900 signals with no indication of the SAR level [Ennamany, et al. 2007].

In China, the expression of genes was investigated in rat neurons [Zhao, et al. 2007]. Exposure was intermittent and lasted 24 hours (GSM 1800, 2 W/kg). Among 1200 genes, 24 genes were up-regulated and 10 down-regulated. This was confirmed by RT PCR. However, the amplitudes of the changes were small (< 1.7-fold using the array and < 4-fold using RT-PCR).

There is today little evidence of major effects of RF on gene expression but several studies are ongoing and one cannot conclude yet about the role of the new high-throughput technique in RF *in vitro* research.

This is also true for the heat-shock proteins (HSP), in view of the most recent reports:

In previous studies using the nematode *Caenorhabditis elegans* the de Pomerai group in the UK had observed induction by weak RF exposure of transgene expression from a small human HSP (hsp16-1) promoter [de Pomerai, et al. 2000]. At the same SAR level the results could not be replicated by the same group [Dawe, et al. 2006]. In a more recent experiment [Dawe, et al. 2007], the same transgenic strain of *C. elegans* was assessed under higher intensity exposure (GSM or CW; 1.8 GHz; ca. 1.8 W/kg; 2.5 hours at 25°C). Under those conditions, the HSP gene was not up-regulated.

HeLa, S3, and E.A. Hy296 cells were exposed to RF signals (American TDMA 847 MHz, 5 W/kg, 1, 2, or 24 hours; or GSM 900, 3.7 W/kg, 1, 2 or 5 hours) and to heat shock (acute: 30 min at 45°C or chronic: 2 h at 41°C) by Vanderwaal and colleagues [Vanderwaal, et al. 2006]. HSP27 phosphorylation was evaluated using 2D gel electrophoresis or using an antibody specific of phosphorylated HSP27. Heat shock induced phosphorylation of HSP27 in all cell types but RF exposure did not.

Human malignant glioblastoma A172 cells were exposed at 2450 MHz at high SAR levels: 5-200 W/kg [Wang, et al. 2006b]. Such exposure induced a temperature elevation and appropriate heat control groups (38-44°C) were thus included. Expression of proteins was determined by Western blotting. Exposure had little or no effect on HSP70 and HSP27 expression, but induced a transient increase in HSP27 phosphorylation above 100 W/kg.

The phosphorylation and overexpression of HSP27 was assayed in Human glioblastoma A172 cells and IMR-90 fibroblasts from fetal lungs by the same group [Hirose, et al. 2007]. W-CDMA and CW signals (0.08 and 0.8 W/kg) were used and no significant differences in the expression of phosphorylated HSP27 were observed immediately after 2-48-hour exposures.

Human T-lymphocyte Jurkat cells and rat primary astrocytes were exposed by Lee and co-workers at 1763 MHz (2 or 20 W/kg) [Lee, et al. 2006]. The expressions of HSPs and activation of MAPKs[4] were monitored. There was no effect of exposure on HSP90, HSP70, and HSP27. Moreover, the phosphorylation status of MAPKs, ERK1/2[5], JNK1/2[6], or p38, was not modified and there was no enhancement of TPA-induced MAPKs phosphorylation.

There are so far only few skin *in vitro* studies published using mobile telephony signals. Sanchez and co-workers [Sanchez, et al. 2007; Sanchez, et al. 2006] have found no effect on HSP expression in human skin cells and reconstructed epidermis, using GSM 900 and 1800 (2 W/kg). Positive controls were obtained using UVB and heat shock. These findings were in agreement with other recent reports by the same group of an absence of effect on the skin of exposed rats.

Cellular functions

Several cellular functions were monitored by Chauhan and co-workers [Chauhan, et al. 2007a] in human-derived cell lines (TK6, HL60 and Mono-Mac-6). Exposure lasted 6 hours (5 min ON, 10 min OFF; 1.9 GHz, pulse-modulated fields; 1 and 10 W/kg). There were no detectable changes in cell viability, cell cycle kinetics, incidence of apoptosis, or cytokine expression immediately after the 6-h exposure period and 18 h after exposure.

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[4] MAPK = Mitogen-activated protein kinase

[5] ERK = Extracellular-signal-regulated kinase

[6] JNK = c-Jun N-terminal protein kinase

Immunology

In Italy, Capri and co-workers exposed peripheral blood mononuclear cells from young and elderly donors to GSM 1800 signals at 2 W/kg with or without mitogenic stimulation [Capri, et al. 2006]. They then analyzed CD25, CD95, CD28 molecules in helper and cytotoxic T lymphocytes. There was no alteration of lymphocyte subpopulations. However, a slight age-related downregulation of CD95, involved in apoptosis, was found in stimulated helper T cells from elderly individuals.

In Israel, Friedman and colleagues have studied the immediate effect of RF exposure (875 MHz, 0-0.11 mW/cm^2, 10 min) on the MAPK cascade in Rat1 and HeLa cells [Friedman, et al. 2007]. They found that ERKs, but not stress-related MAPKs, were rapidly activated under exposure. Using further tests they concluded that ROS were produced that in turn indirectly activated the ERK cascade. However, the dosimetry of the exposure system was not done as no SAR level was measured or calculated and the uniformity of SAR was not determined. It is therefore very difficult to assess the validity of the findings and even more that of the suggested mechanism.

Ornithine decarboxylase (ODC)

Following the report of increased activity of the ornithine decarboxylase (ODC) enzyme after an 8-hour exposure of cells to RF signals at 2.5 W/kg [Penafiel, et al. 1997], several replication studies have been performed. Recent work on L929 murine fibroblasts showed that a 1°C temperature increase (RFR or conventional heating) decreased ODC enzyme activity [Hoyto, et al. 2007; Hoyto, et al. 2006]. When cells were isothermally exposed at SAR up to 15 W/kg, different outcomes in ODC activity were found according to the type of setup used, but on the whole, the previous results could not be replicated.

Concluding remarks on RF cell studies

A large number of in vitro studies have been published recently investigating various outcomes, e.g. effects on reactive oxygen species, genotoxicity, apoptosis, gene expression, immunology, and enzyme activity. Most of these studies have not demonstrated any effects of RF exposure on the studied outcomes, including also attempts to replicate the genotoxic effects observed in the REFLEX European programme. Additional studies are currently underway, for example on gene expression. Some other areas need further investigation, such as effects of RF exposure on apoptosis in more cell types including primary cells.

Animal studies

Carcinogenicity

Tillman et al. [Tillmann, et al. 2007] evaluated carcinogenicity of both a GSM (Global System for Mobile Communication) signal at 902 MHz and a DCS (Digital Personal Communications System) signal at 1747 MHz in B6C3F1 mice. 50 male and 50 female mice per group were exposed for 2 h per day, 5 days per week over a period of 2 years at whole-body averaged SAR levels of 0.4, 1.3, 4.0 W/kg , or were sham exposed. No significant increase in the incidence of any particular tumour type in the RF exposed groups was observed. Interestingly, in both studies (both RF signals) the incidence of liver adenomas in males decreased with increasing exposure level, with a statistically significant

difference between the highest exposure and the sham exposed group. Comparison to published tumour rates in untreated mice revealed that the observed tumour rates were within the range of historical control data. In conclusion, the study produced no evidence that exposure at whole body absorption rates of up to 4.0 W/kg increased the incidence or severity of neoplastic or non-neoplastic lesions, or resulted in any other adverse health effects.

In an 18-month carcinogenicity study by Oberto et al. [Oberto, et al. 2007], Pim1 transgenic mice were exposed for 1 h/day, 7 days/week to pulsed 900 MHz (pulse repetition rate 217 Hz) RF radiation at a whole-body SAR of 0.5, 1.4 or 4.0 W/kg. 50 animals per sex per group were exposed, sham-exposed or used as cage controls. The experiment was a replication and an extension of a previously published study that reported an increase in lymphomas in female Pim1 transgenic mice after exposure to a similar RF signal [Repacholi, et al. 1997]. There were several methodological improvements compared to the Repacholi et al. study, including use of several exposure levels, well-defined dosimetry and more uniform exposure (restrained animals) and necropsy and extensive histopathology of all animals. Compared to the sham-exposed controls, survival was reduced in the animals exposed to RF radiation. The intergroup differences were statistically significant in the male animals, but there was no trend with increasing exposure level (lowest survival at 0.5 W/kg). No increase in lymphoma incidence was observed in the RF exposed groups. Concerning other neoplastic findings, harderian gland adenomas were increased in male mice, with a significant dose-related trend ($p<0.01$). However, this trend was not supported by the findings on female animals, in which no tumours in the highest exposure groups were observed. The statistical analysis used in this study can be criticized. The cage control and the sham-exposed control groups were combined for statistical comparisons, which is not a valid procedure given the differences in body weight development and tumour incidence between the cage control and sham control animals (these differences are most likely related to restraint of the sham control animals). However, based on the data reported in the paper, a different analysis strategy (comparison to the sham control group only) would not essentially change the interpretation that there was no effect of RF radiation on tumour incidence at any site. The reduced survival in RF-field-exposed animals is not thoroughly discussed by the authors; this finding remains unexplained and difficult to interpret without detailed information about the causes of death.

Yu et al. treated 100 female Sprague-Dawley rats per group with a single dose of 7,12-Dimethylbenz(a)anthracene to induce mammary tumours and then exposed the animals to 900 MHz GSM signals [Yu, et al. 2006]. The exposure groups included cage controls, sham-exposed controls and three exposure groups with SARs of 0.44, 1.33 and 4.0 W/kg.The exposed and sham exposed animals were restrained during exposure. The rats were weighed and palpated weekly for the presence of mammary tumours and were killed at the end of the 26-week exposure period. All mammary glands were examined histologically. No significant differences in the final incidence of mammary tumours, time to development of palpable tumours, tumour multiplicity, or tumour size were observed between RF-exposed and sham-exposed groups. There was a statistically non-significant ($p=0.058$) tendency for reduction of mammary adenocarcinoma incidence in the lowest (0.44 W/kg) exposure group compared with the sham-exposed group. Significant differences were observed between the cage controls and the other experimental groups, with increased body weight and higher number and more rapid development of mammary tumours (malignant plus benign) in the cage control group. These differences are most likely related to restraint of the sham control and RF-exposed animals. The statistical

analysis of tumour appearance (which was done by Cox regression) was apparently done without making a difference between tumours observed during the study by palpation and tumours detected in histopathological evaluation. While this could in principle mask differences between the groups (also small non-palpable tumours are detected in histopathology), the data shown in the paper suggest that a different statistical analysis would not essentially change the conclusion that RF radiation did not promote mammary tumour development.

Heikkinen and co-workers investigated the possible co-carcinogenetic effects of the long-term daily treatment of rats with MX[7] [Heikkinen, et al. 2006], a known bacterial mutagen and a multi-site carcinogen in rats, combined with repeated RF exposure over a prolonged period of time. Beginning at 7 weeks of age, MX-treated animals were exposed or sham-exposed using a radial waveguide system to pulsed 900 MHz (GSM) signals for 2 h per day, 5 days per week for 2 years at whole-body SARs of 0.3 and 0.9 W kg^{-1}. The authors carried out a full histopathological examination of these animals. MX-exposed animals (sham RF-exposed) showed significantly reduced survival and increased levels of malignant and benign tumours, reaching statistical significance in some cases, compared to cage-control animals. RF exposure did not significantly affect mortality, the organ-specific incidence of any tumour type or the total number of tumours. Thus the data do not support a co-carcinogenic effect of prolonged low-level GSM RF exposure.

Sommer and co-workers investigated the development of lymphoma in an experimental lymphoma model, the AKR/J mouse [Sommer, et al. 2007]. Unrestrained mice, 160 animals per group, were chronically sham-exposed or exposed in identical exposure systems to a generic UMTS test signal for 24 h/day, 7 days/week at a SAR of 0.4 W/kg. Additionally, 30 animals were kept as cage controls. The animals were checked visually each day and were weighed and palpated weekly to detect swollen lymph nodes. Starting at the age of 6 months, blood samples were taken from the tail every 2 weeks to perform differential leukocyte counts and to measure the hematocrit. Visibly diseased animals or those older than 43 weeks were killed humanely, and tissue slices were examined for metastatic infiltrations and lymphoma type. Cage control animals had a significantly lower growth rate than those kept in the radial waveguides. Incidence of lymphoma, survival time and the severity of the disease, indicated that there was no effect from exposure to RF radiation. Cage control animals had significantly lower body weights and higher occurrence of metastatic infiltrations in liver and meninges that the other groups. This difference was most likely related to different housing conditions and stress level.

Zook and Simmens investigated further possible promoting effect of RF radiation on ethylnitrosourea (ENU)-induced brain tumours in Sprague-Dawley rats [Zook and Simmens 2006]. In a previous study, they had found a statistically nonsignificant trend for shortened latency of ENU-induced brain tumours [Zook and Simmens 2001]. In the present study, latency and other characteristics of neurogenic tumours were investigated in the progeny of pregnant Sprague-Dawley rats treated with 6.25 or 10 mg/kg of ENU. The 1080 offspring were randomized equally by number, sex and ENU dose into pulsed RF, sham and cage control groups. The rats were exposed to the RF field (MiRS signal, 860 MHz, 11.1 pulses per second) 6 h/day 5 days/week at a SAR of 1.0 W/kg averaged over the brain (0.27-0.42 W/kg averaged over the whole body). The animals were restrained during the exposures. An equal number of rats from each group were killed every 30 days

[7] 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone

between the ages of 171 and 325 days; 32 rats died and 225 rats were killed when they were moribund. All rats were necropsied and the brain and spinal cord were examined histopathologically. The examinations revealed 38 spinal cord tumours, 191 spinal nerve tumours, 232 cranial nerve tumours, and 823 brain tumours. No evidence was found of RF radiation effects on the incidence, malignancy, volume, multiplicity, latency or fatality associated with any kind of neurogenic tumour. Body weight was higher in the cage control animals than in the other groups, which is most likely related to restraint of the exposed and sham-exposed animals.

In conclusion, six recent studies with rodents have evaluated carcinogenicity of RF electromagnetic fields similar to those emitted by mobile phones. The studies consistently report lack of carcinogenic effects in several different animal models including classical bioassays, studies using genetically predisposed (transgenic) animal models and cocarcinogenicity studies involving combined exposure to RF fields and known carcinogens. The new studies are consistent with results from previous studies, and add to the evidence that the RF fields with characteristics similar to those emitted by mobile phones are not carcinogenic in laboratory animals. Some of the new studies have also used exposure levels up to 4 W/kg, which is high compared to most previous studies. Thus, these studies provide a useful addition to the database available for health risk assessment.

Genotoxicity

Two recent studies have evaluated genotoxicity of mobile phone emissions in rodents exposed to RF electromagnetic fields.

Juutilainen et al investigated the genotoxicity of long-term exposure to three different mobile phone signals of one common laboratory strain of mouse (CBA/S) [Juutilainen, et al. 2007], and a transgenic strain (K2) containing several copies of a human gene ornithine decarboxylase, which is involved in cell proliferation, along with their normal littermates, at three different whole-body SARs. Blood samples for micronucleus analysis were taken at necropsy from animals which had been part of two long-term bioassays of RF co–carcinogenesis. In the first experiment [Heikkinen, et al. 2001], CBA/S mice were exposed or sham-exposed either to an analogue 902.5 MHz mobile phone signal at a whole-body SAR of 1.5 W kg^{-1} or to a pulsed 902.5 MHz GSM mobile phone signal at a whole-body SAR of 0.35 W kg^{-1}, for 1.5 h per day, 5 days per week, for 78 weeks. During the first 3 weeks of RF exposure the mice also received a total dose of 4 Gy x-rays in order to induce lymphomas and other tumours. In the second experiment [Heikkinen, et al. 2003], female transgenic (K2) mice and their non-transgenic littermates were exposed or sham-exposed either to 902 MHz GSM RF or to 894 MHz DAMPS mobile phone signals at a whole body SAR of 0.4 W kg^{-1} for 1.5 h per day, 5 days per week, for 52 weeks. The mice were also exposed three times a week to an ultraviolet radiation (UVR) dose of 1.2 MED (minimum erythemal dose) in order to induce skin tumours. Juutilainen et al report that no effects on micronucleus frequency were seen that had resulted from long-term RF exposure [Juutilainen, et al. 2007].

Verschaeve et al. assessed DNA damage in white blood cells, brain and liver tissue samples using the alkaline comet assay [Verschaeve, et al. 2006], and determined the micronucleus frequency in immature erythrocytes in the same animals as those used by Heikkinen and co-workers, described above [Heikkinen, et al. 2006]. Sham-exposed animals, which had been treated with MX, had increased DNA damage only in brain tissue cells compared to cage-control animals. There was no evidence that RF exposure significantly

increased levels of DNA damage or micronucleus frequency in any tissue and so there was no support for a co-genotoxic effect of RF.

In conclusion, two recent studies reported no increase in micronuclei or DNA damage (evaluated by the comet assay) in rats and mice in experiments that involved SAR values up to 1.5 W/kg and combined exposure to known genotoxic agents. These results are consistent with the majority of previous *in vivo* and *in vitro* studies, which have generally not shown genotoxic effects from exposure to RF radiation. In particular, the results did not confirm previous findings suggesting increased micronucleus frequency in cells and animals exposed to RF radiation. Strengths of these studies were the use of whole animals and long exposure times.

Nervous system effects

Brillaud et al. measured the level of Glial Fibrillary Acidic Protein (GFAP) [Brillaud, et al. 2007], a marker of astrocyte injury, 2, 3, 6 and 10 days after a single 15-min exposure to a GSM-type 900 MHz field at brain averaged SAR of 6W/kg. 9 exposed animals and 6 sham-exposed animals were killed at each time point and several brain areas were examined for GFAP immunohistochemically. A statistically significant increase of GFAP stained surface area was observed 2 days after exposure in the frontal cortex and the caudate putamen. A smaller statistically significant increase was noted 3 days after exposure in the same areas and in the cerebellum cortex. The results confirmed similar findings observed at 72 h after exposure at 6 W/kg [Mausset-Bonnefont, et al. 2004], and provided additional data of the time-dependence of the effect. No temperature increase was observed during the 15-min exposure on skin below the antenna, but local temperature changes, particularly at tissue interfaces, remain a possible explanation for the observations. The relevance of these findings to human risk assessment is unknown at present; additional experiments to examine the mechanisms and dose-response of these effects would be valuable.

Kumlin et al. investigated the effects of prolonged 900 MHz mobile phone radiation on the developing central nervous system [Kumlin, et al. 2007]. Young (~ 3 week old) rats were exposed or sham-exposed to 900 MHz GSM mobile phone radiation at average whole-body SARs of 0.3 or 3.0 W kg^{-1} for 2 hours per day, 5 day per week for 5 weeks. A variety of behavioural tests were carried out following exposure and brain tissue histology was examined. The immunohistochemical assays did not reveal any significant changes in brain tissue. In particular, the results do not support the observations of Salford et al. of degenerative changes following a single RF exposure [Salford, et al. 2003], including increased pycnotic nuclei and permeability of the blood-brain barrier. No effects were seen on the performance of the open-field test, the elevated plus maze test or the acoustic startle response test. However, the authors did find an improved task acquisition and retention of the water maze task, a test of spatial and working memory, in the exposed juveniles in contrast to previous reports of either reduced performance (eg [Lai and Singh 2004]) or no effect (eg [Sienkiewicz, et al. 2000]) seen in older animals.

Results from previous animal studies are inconsistent: while many studies have found no evidence of RF radiation effects on the nervous system, a few studies have reported changes in behavioural tests, EEG activity and neurotransmitters [Sienkiewicz, et al. 2005]. The findings of the two new studies underline the importance to conduct further studies on nervous system effects. In particular, additional studies should address possible effects from long-term exposure of juvenile animals and investigate dose-response of positive findings reported above the current exposure limits.

Concluding remarks on RF animal studies

Six recent studies on carcinogenicity, some with higher exposure levels than previously used, consistently report lack of carcinogenic effects, and two studies on genotoxicity report no increase in micronuclei or DNA strand breaks after RF exposure. These results are consistent with the majority of previous studies.

Human laboratory studies

Volunteer studies carried out with regard to mobile phone use have investigated the effects of mobile phone type RF radiation at levels generally assumed to be too low to induce significant heating. Important factors in the experimental design of many recent studies include the use of double-blind procedures, and crossover and counter-balanced protocols. Double-blind procedures apply when both the experimenters and subjects are unaware of the exposure status of the subjects, and so are less likely to be influenced by any expectation of a particular outcome; single-blind procedures, often used in early studies, are where only the subject is unaware of their exposure status. A crossover design is where subjects are both exposed and sham exposed in different parts of the experiment, so that they act as their own controls (also known as a within-subjects or repeated measures design). This procedure minimises the effects of intrinsic differences between subject groups, such as might occur between a sham group and an exposed group, which could affect the experimental outcome. A counter-balanced protocol is where all possible orders of exposures are used, with equal numbers of subjects experiencing each order. This counteracts any effect of time-dependency on the subjects' responses, resulting for example from improving in task performance or from loss of attention during the course of a study.

Brain physiology

In the field of cognitive neuroscience, it is generally assumed that changes in regional cerebral blood flow (rCBF) reflect localised changes in brain neural activity. Such changes have been used to measure the effects of RF radiation on brain physiology. Other measures used to assess the effects of RF include recordings of brain electrical activity and the responses of brain tissue to interventions such as transcranial magnetic stimulation.

Aalto and co-workers [Aalto, et al. 2006] investigated the effects of exposure and sham exposure, presented in a double-blind, counterbalanced order, to 902 MHz GSM-like RF radiation on rCBF in 12 male volunteers. The peak SAR in 10 g of tissue under the phone antenna was estimated to be 0.7 W kg^{-1}. The mobile phone was supplied by an external power source in order to avoid auditory stimulation from the phone battery, thought to have influenced a previous study by these authors (Haarala et al, 2003a). During both exposure conditions, subjects continuously performed a simple working memory task. Positron emission tomography scans were carried out during RF exposure and sham-exposure. The authors reported a statistically significant decrease in rCBF in the inferior temporal cortex, just below the RF antenna, and increases in regions in the prefrontal cortex during RF exposure, compared to the sham exposure conditions. However, there were no effects on the accuracy and reaction times for the working memory task. Nevertheless, the authors note that their results are consistent with a localised RF-induced increase in neuronal activity in the prefrontal, but not in the temporal cortex.

Inomata-Terada and colleagues [Inomata-Terada, et al. 2007] investigated the short-term effects of exposure to 800 MHz RF radiation typical of Japanese mobile phones on the responses of the motor cortex, and other regions in the motor pathway to transcranial magnetic stimulation in ten volunteers. The SAR averaged over 10 g brain tissue was 0.05 W kg^{-1}. Two multiple sclerosis patients who were susceptible to a corticospinal bock induced by a hot bath were also included in the study. The authors applied a single pulse transcranial magnetic stimulation to the motor cortex, brain stem or cervical motor nerve and measured the motor-evoked potentials in a target muscle in the hand before and after a 30 min mobile phone exposure or sham exposure of the left side of the head in order to examine possible RF effects on the integrity of the motor conduction pathway. In addition, they applied a paired pulse transcranial magnetic stimulation to the motor cortex, in which a below threshold conditioning pulse is followed 1-5 ms later by an above threshold test pulse (see IEGEMF 2006), before and after exposure in order to examine possible RF effects on intracortical inhibition. This is mediated by small interneurons that are relatively susceptible to metabolic stress such as hypoxia compared to the larger motor cortical output neurones. The authors found no effect of mobile phone radiation on any of the responses investigated in the healthy volunteers. In addition, no effects were seen in the responses of the MS patients. The authors note that the small number of subject may have limited the power of the study to detect subtle effects. In addition, it may be recalled that Ferreri and co-workers [Ferreri, et al. 2006], in a similar study of RF effects on the motor cortex, using transcranial magnetic stimulation, reported small RF-induced changes in cortical excitability and inhibition, although of only borderline statistical significance (see IEGMP, 2006).

Electrical activity of the brain

The scalp-recorded electroencephalogram (EEG) is a reflection of synchronous activity in relatively large populations of cortical neurons. The 'spontaneous' EEG of awake subjects is conventionally divided into a number of frequency bands, the relative amounts of activity in which depends upon the psychological state of the subject and the nature of the cognitive function in which the subject is engaged, although their functional significance is poorly understood.

Vecchio and co-workers examined the extent to which exposure to a GSM mobile phone signal affected the functional coupling of cerebral EEG rhythms between different brain regions [Vecchio, et al. 2007]. Ten male volunteers were exposed or sham exposed to 902 MHz GSM RF radiation from a mobile phone situated on the left side of the head in two 45 min sessions separated by one week, following a double-blind crossover design. The maximum power output of the phone was 2 W (average 0.25 W). The authors examined the spectral coherence of the EEG signals derived from the right and left cerebral hemispheres; comparing specifically the EEG recordings from frontal, temporal and parietal pairs of electrodes on each cerebral hemisphere. Vecchio et al [2007] reported that exposure enhanced the interhemispheric coupling of alpha (8-12 Hz) rhythms between the temporal brain regions, but diminished coupling between the frontal areas, and suggested that this might reflect changes in cognitive processes associated with these regions. However, this last supposition was not tested experimentally, so possible functional effects of these changes remain unclear.

The following two groups combined an examination of the effects of GSM-type RF radiation on EEG frequency bands with cognitive testing. Regel and colleagues [Regel, et al. 2007] exposed 24 male volunteers for 30 min to pulsed GSM 900 MHz or continuous

wave 900 MHz (spatial peak SAR of about 1 W kg^{-1} averaged over 10 g of tissue in both cases), or the sham exposure. The three experimental conditions were applied at weekly intervals in a double-blind, randomised and counterbalanced crossover design. During exposure, the subjects performed three working memory tasks of differing complexity. The EEG was recorded before exposure (baseline), immediately afterwards, or 30 or 60 min after exposure. The authors reported that the pulse-modulated GSM RF radiation increased spectral power in the 10.5-11 Hz range only after 30 min, and decreased spectral power at 12 Hz only after 60 min. In addition, increased reaction time and accuracy of performance was reported during exposure in the most demanding working memory task. However, no effects on EEG or behavioural performance were seen during or after exposure to continuous wave 900 MHz. Regel et al [2007] conclude that their present results of pulsed RF affecting alpha EEG activity are consistent with the results from previous studies by other authors [Croft, et al. 2002; Curcio, et al. 2005; D'Costa, et al. 2003; Huber, et al. 2002].

Krause and co-workers [Krause, et al. 2007] replicated and extended earlier studies [Krause, et al. 2004; Krause, et al. 2000a; Krause, et al. 2000b] in which the effects of a 902 MHz GSM signal on event-related desynchronisation/synchronisation (ERD/ERS) of four EEG frequency bands were investigated during the performance of an auditory and a visual memory task. The SAR value averaged over 10 g tissue was estimated to be 0.7 W kg^{-1}. The earlier studies found some effects of RF on the ERD/ERS responses in the 8-10 Hz EEG frequency range, but Krause et al [2004] was not able to replicate this. Krause et al [2007] set out to partially replicate their earlier studies, this time comparing the effects of sham, pulsed and continuous wave GSM exposure of the left and right sides of the head. Two groups of 36 volunteers participated; one group performed the auditory memory task and the other the visual memory task. The authors used a double-blind protocol, and the exposures were counter-balanced across subjects. The authors found that there were no effects of exposure condition on either behavioural task, and that only modest and rather variable changes were seen in the 8-12 Hz EEG frequency range. These results supported earlier observations that any effects on EEG were subtle and difficult to replicate, and that, as in the previous studies, these did not affect performance the behavioural tasks.

Sleep

Hung et al examined the effects of the ‘talk’, ‘listen’ and ‘standby’ pulse modulation modes of 900 MHz GSM RF signals [Hung, et al. 2007], which differ in their ELF (2 Hz, 8 Hz and 217 Hz) spectral components, on sleep onset identified by EEG analysis. The authors used a GSM phone set to transmit at 12.5% of the maximum power and adjusted to simulate each of the three specific modes. SARs, averaged over 10 g of tissue, were estimated to be 0.1 W kg^{-1} (talk), 0.01 W kg^{-1} (listen) and 0.001 W kg^{-1} (standby). At weekly intervals, ten volunteers, restricted to a 6 hr sleep schedule the previous night, were randomly exposed to the talk, listen, standby and sham (no signal) modes for 30 min at 13.30 h. The exposures were single blind and counterbalanced between participants. Following exposure, the room was darkened, and a 90 min sleep opportunity followed. Subjective assessments of sleepiness, and EEG recordings were made before, during and after exposure. The authors reported that sleep onset after exposure in the talk mode was significantly delayed compared to the listen and sham modes, and that this differentiation was apparent in the changes in EEG, particularly in the 1-4 Hz frequency band which is sensitive to sleep onset. The authors suggest that 2, 8 and 217 Hz GSM

modulation may differentially affect sleep onset. The number of subject in this study was however quite low.

A second experiment investigating the effects of exposure to 900 MHz GSM mobile phone RF radiation reported a lack of effect on sleep and on cognitive function [Fritzer, et al. 2007]. These authors exposed or sham exposed 20 volunteers to 900 MHz GSM RF signals, which included pulse modulation at 2 Hz, 8 Hz, 217 Hz and 1.7 kHz, each night for 6 consecutive nights whilst they slept, recording their EEG during sleep, and applying a battery of tests of cognitive function before and after sleep on the first and last night of exposure. The maximum SAR averaged over 1 g of tissue was estimated to be approximately 1 W kg^{-1}. The tests examined attention, information processing, visual discrimination and included various tests of memory and learning. The EEG recording and cognitive function tests were also applied the night before the first exposure, in order to generate baseline data. The authors found no short term (1 night) or cumulative long term (6 nights) effects of night-time GSM exposure on a number of sleep parameters including sleep onset latency, on the mean EEG power spectrum in REM and non-REM sleep, and on any of the battery of cognitive tests.

Cognitive studies

Cinel and co-workers [Cinel, et al. 2007] carried out a replication study of the observation by Maier et al [Maier, et al. 2004] of a decrement in the performance of an auditory discrimination task following a 50 min exposure to a 900 MHz GSM-type RF field (see [IEGEMF 2004]). As in the original study, the participants performed the auditory discrimination task in two sessions, being exposed under double blind conditions to RF in one session, and were sham exposed in the other session. Cinel et al [2007] however used a much larger number of volunteers (168 vs 11) and included in their study an investigation of any differential effect between GSM modulated 888 MHz RF and continuous wave RF (2 x 84 volunteers per group) and for any lateralising of the effect, with the phone placed on the left or right side of each subject's head (4 x 42 per group). The SAR averaged over 10 g of tissue was estimated to be 1.4 W kg^{-1}. Analysis of the results indicated that there was no effect of GSM or CW RF radiation on task performance, nor was there any effect due to laterality of exposure.

Haarala and colleagues [Haarala, et al. 2007] also compared the effects of exposure to of the right or left side off the head to continuous wave 902 MHz RF or GSM RF on cognitive function using the same tests used in their previous studies [Haarala, et al. 2003; Haarala, et al. 2004; Koivisto, et al. 2000a; Koivisto, et al. 2000b]. These included simple reaction time and vigilance tasks, a mental arithmetic subtraction task, a choice reaction time task, and a visual memory task (n-back task) in which the working memory load could be varied. Testing was conducted in three sessions (GSM RF, continuous wave RF and sham) separated by one week and in each exposure session, both sides of the head were exposed. The SAR averaged over 10 g of tissue was 0.7 W kg^{-1}. The experimental design was double-blind and counterbalanced across both the exposure conditions and side of the head exposed; each of the 36 male subjects acted as their own control. The authors reported that there were no statistically significant effects of exposure condition and laterality of exposure on any measure of cognitive performance.

Two recent studies by Terao and colleagues in Tokyo examined the effects of 30 minute exposure to 800 MHz PDC mobile phone signals characteristic of Japanese handsets on visuo-motor choice reaction time, and on oculomotor performance [Terao, et al. 2006; Terao, et al. 2007]. Both studies used double-blind, counterbalanced crossover protocols.

In both studies, the two test sessions (RF exposed and sham) were separated by a period of 7 days. Terao et al [2006] investigated effects of RF on a the performance of a task known to involve cognitive processing in certain cortical regions such as the motor cortex in which 16 subjects were given variable amounts of relevant information about the correct response before being required to press one of two buttons with the left or right hand after a 'go' signal. The task was performed before and after the 30 min exposure, during which time subjects held the phone by hand next to their preferred ear. The SAR averaged over 10 g brain tissue was 0.05 W kg^{-1}. There were no significant effects of exposure on reaction time.

The control of visual spatial attention and eye movements share many underlying cortical structures. The second study by this group [Terao, et al. 2007] investigated the effects of PDC mobile phone signals on fast eye movements known as saccades using a similar experimental protocol to that described above. Saccades are very fast, simultaneous movements of both eyes in the same direction and are involved in searching visual scenes and orienting towards novel or salient stimuli. The authors examined three oculomotor paradigms in 10 subjects: the visually guided saccade, gap saccade and memory guided saccade; a visual detection task was also included in order to monitor arousal and spatial attention. The authors reported that there were no significant effects of RF exposure on any of the saccade parameters, or on the reaction time in the visual detection task. However, Terao et al [2007] acknowledge that the number of subjects was quite low, reducing the power of the study.

Subjective symptoms

A sub-group of the population report experiencing a variety of symptoms such as headaches in the vicinity of RF sources. Studies have recently been carried out by two groups.

Oftedal and colleagues [Oftedal, et al. 2007](2007) investigated the occurrence of headaches in 17 individuals who report themselves sensitive only to mobile phone RF radiation in a double-blind RF provocation study with a counter-balanced crossover design. The initial volunteer group was 42, of which 24 were considered eligible following an open provocation test where the subjects were aware of their exposure to mobile phone RF. A further 7 did not complete the study for various reasons, leaving a total of 17 participants. Each of the 17 subjects took part in a maximum of four pairs of 2 hour experimental trials, separated by at least 2 days; each trial comprising a 30 min exposure to 902 MHz GSM RF radiation and a 30min sham exposure with a counterbalanced order of exposure presentation. The SAR averaged over 10 g tissue around the ear was 0.8 W kg^{-1}. Subjects recorded their symptoms before, during and after each treatment; heart rate and blood pressure were also monitored during this period. The authors reported that the degree of discomfort and headache experienced during and after sham exposure was slightly, but not significantly, higher than that experienced after RF exposure. In addition, subjects were unable to indicate whether they had been exposed. There were no effects of exposure on systolic or diastolic blood pressure, or on heart rate. Oftedal et al [2007] concluded that the most likely explanation for symptoms experienced when the subjects know their own exposure status is that of prior expectations, ie a 'nocebo' effect.

Eltiti and co-workers [Eltiti, et al. 2007] carried out a similar study to that described above but which investigated the effects of GSM and UMTS exposure on the incidence of a variety of symptoms and physiological responses in people who identified themselves as sensitive to mobile phone base station signals, compared to the incidence in people who did not regard themselves as RF sensitive (the controls). In some respects, the study

follows on from studies by Zwamborn and co-workers [Zwamborn, et al. 2003](2003) and Regel and co-workers [Regel, et al. 2006] of GSM and UTMS base station signals on well-being in RF-sensitive and non-sensitive people (see IEGEMF, 2004, 2006). Briefly, Zwamborn et al [2003] found that exposure to UMTS base station signals reduced subjective well-being in both RF-sensitive and non-sensitive subjects, but this effect was not replicated in the study by Regel et al [2006], which had an improved experimental design that included a more uniform and reproducible exposure, better dosimetry, improved matching with respect to gender, age etc between subject groups, and a better control over possible circadian and carry-over effects between sessions (see IEGEMF, 2006).

In the present study, RF sensitive and control subjects were exposed to three conditions separated by one week: GSM signals containing both 887 and 1877 MHz broadcast frequencies, 2020 MHz UMTS signals and a sham exposure. In each case, the power flux density over the area where the subject was seated was 10 mW m^{-2}. As in the study by Oftedal et al [2007], this followed an open provocation test (session 1) which confirmed the hypersensitivity of the self-identified RF sensitive individuals. The subsequent exposure to GSM, UMTS or sham conditions (sessions 2, 3 and 4) was carried out using a double-blind, counter-balanced crossover design. The authors had planned on recruiting 132 participants per group (RF-sensitive and control) as the study proceeded, and so this number was pre-programmed into the exposure system control computer. In fact, only 58 sensitive individuals and 115 controls participated and so the study did not achieve a balanced exposure order in the group of sensitive individuals. Overall, Eltiti et al [2007] reported that there were no effects of exposure on a number of subjective measures of well-being in the control group. However, arousal levels were higher in the sensitive group during UMTS exposure compared to the sham condition, but not for the GSM exposure, which seemed to support the earlier findings by Zwamborn et al [2003]. A closer examination of the data revealed that a high proportion (45.5% compared to an expected 33.3%) of sensitive individuals were exposed to UMTS in the first main experimental session (session 2), and that arousal was generally higher in sensitive individuals in this session, regardless of the exposure condition. This response was therefore considered likely to be the result of exposure order rather than a true effect of UMTS exposure. Otherwise, there was no significant effect of exposure to GSM or UMTS RF radiation seen in either group for a number of physiological measures such as heart rate and skin conductance compared to sham conditions. In addition, as has been observed by other authors [see IEGEMF 2006], sensitive individuals were unable to detect the presence of an RF field during double-blind exposure, but reported more symptoms of a greater severity than control individuals, regardless of their exposure status.

Heart rate, blood pressure and heart rate variability

In principle, '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, leading to possible effects on heart rate, heart rate variability and on blood pressure.

Parazzini et al focussed their investigation of possible 900 MHz GSM RF radiation effects on heart rate variability in 26 volunteers [Parazzini, et al. 2007]. The local maximum SAR below the phone antenna was estimated to be less than 0.02 W kg^{-1} averaged over 10 g of brain tissue in the hypothalamus and brain stem regions involved in the control of heart rate variability. Frequency and time-domain analysis of heart rate variability is thought to provide quantitative information regarding the sympathetic and parasympa-

thetic control of heart rate by the autonomic nervous system. Heart rate variability data were collected during two different sessions, one with a real RF exposure and the other with a sham exposure. These sessions were performed on separate days in a random order following a double blind experimental design. During each 26 min session, the subject underwent a standard rest-to-stand protocol, thought to elicit sympathetic activity. Data analysis revealed that RF exposure did not affect most heart rate variability parameters; however, a few weak but statistically significant changes were seen in some minor indices of heart rate variability such as an increase in the low frequency component as subjects moved into the stand position. The authors suggest this might indicate an augmentation of sympathetic activity. However, it is not clear whether the analysis allowed for multiple testing, and so the significance of these minor changes may have been overestimated.

Barker et al examined the effects of both TETRA and GSM mobile handset signals on blood pressure and heart rate variability in 120 subjects [Barker, et al. 2007]. In this study, the subjects were seated and blood pressure and heart rate were recorded during a 20 min pre-exposure period, and a 40 min double-blind RF exposure or sham exposure session. Four different sets of RF signals were applied in addition to the sham exposures: GSM modulated signals, GSM carrier wave, TETRA modulated, and TETRA carrier wave. Peak SARs in 10 g of tissue were less than 1.4 W kg^{-1}, ie less than 70% of the ICNIRP public exposure limit on local SAR in the head and trunk [ICNIRP 1998]. The authors found no effect of any RF signal on mean arterial blood pressure, or on any measure of heart rate variability, either in the low frequency or high frequency bands. However, mean arterial blood pressure was reduced (by ~ 0.7 mm Hg) for GSM sham exposures and the authors speculate that this might have resulted from a slight increase in the operating temperature of the handset when in this mode.

Concluding remarks on human laboratory studies

Most recent volunteer studies have investigated the effects of GSM mobile phone type RF radiation. In general, the recent, methodologically more rigorous studies do not replicate the positive findings from smaller, less rigorous studies published a few years ago, but a few positive effects are reported.

In nearly every experiment, the phone is situated near the ear in a position that simulates normal phone use. These exposures, normally characterised by estimates of local peak and average SARs, complied with the ICNIRP public limits on localised SAR of less than 2 W kg^{-1} averaged over any 10 g of tissue in the head and trunk. Most RF deposition from mobile phone use is to the skin and muscle tissue around the ear [Dimbylow and Mann 1994] with little absorbed by the underlying superficial layer of cortical tissue. It seems that only four studies cite SAR in brain tissue [Inomata-Terada, et al. 2007; Parazzini, et al. 2007; Terao, et al. 2006; Terao, et al. 2007]. Only in the latter case however, is any correlation made with the experimental outcome (heart rate variability). Generally, the neural pathways involved most tests of brain function are likely to be widespread making it difficult to relate local SAR and experimental outcome.

The recently published cognitive studies are mostly negative; several report a lack of effect from both pulsed and CW RF radiation. In addition, several studies examining RF effects on regional cerebral blood flow, on the brain electrical activity (EEG) and on sleep report modest changes in some parameters but little concomitant effect on cognitive function. No effects were seen on motor cortex function, using transcranial magnetic stimula-

tion techniques. Several studies of brain electrical activity reported slight RF-induced changes in the alpha (8-12 Hz) EEG rhythm, as has been observed previously by other authors. One study also reported increased reaction times and accuracy in the performance of the most demanding working memory task; another found no effect on the performance of two memory tasks.

For sleep, heart rate variability and blood pressure, two studies find no effect, and two report positive effects. One study involving a small numbers of subjects reported that sleep onset was delayed following exposure from a mobile phone in the talk mode, and another study found modest changes in some minor indices of heart rate variability.

With regard to hypersensitivity, the recent studies examining the effects of GSM and UTMS RF radiation support the observation made previously (see IEGEMF 2006) that RF-sensitive individuals report symptoms of greater severity than non-sensitive individuals, but these are not correlated with exposure and may reflect the conscious expectation of such effects.

Recent epidemiological studies

Mobile phone studies

Interphone

An analysis based on the German Interphone study with 97 cases and 194 matched controls revealed no increased risk of acoustic neuroma related to mobile phone use (OR=0.7, 95% CI 0.4-1.2) [Schlehofer, et al. 2007]. Decreasing rather than increasing trends were shown for time since first use, cumulative number of calls and cumulative duration of calls. The small number of exposed cases (N=29) limited the value of the study.

The results of the Norwegian Interphone study on mobile phone use and risk of intracranial tumours were published separately [Klaeboe, et al. 2007] . Previously, those related to acoustic neuroma and glioma have been reported in joint analyses. The Norwegian study had a higher proportion of telephone interviews compared with other centres (nearly half of case interviews). No increased risk of meningioma was found for regular mobile phone use, nor association with time since first use, cumulative number or duration of calls based on 207 cases (96 regular mobile phone users). Similar risk estimates were found for ipsilateral and contralateral use. No risk estimates were shown for mobile phone usage for more than 10 years, but the category with the longest exposure duration was only 6 or more years. The report does not substantially add to the literature.

Other studies

A nationwide population-based case-control study of testicular cancer [Hardell, et al. 2007a] was conducted with 888 cases (542 seminoma, 346 non-seminoma) and 870 individually matched controls. Unconditional logistic regression was used despite the matched design. Exposure assessment was based on questionnaires several years after diagnosis, with response proportion of 91% among cases alive and 89% among controls. Of the cases 42% and 41% of the controls had used a mobile or cordless phone for at least one year. Non-significantly elevated ORs of seminoma were reported in association with use of both analogue (OR=1.2; 95% CI 0.9-1.6) and digital phones (OR=1.3; 95% CI 0.9-1.8), but no association was seen with amount of use or keeping a phone on the waist

while on standby. The results do not indicate an increased risk of testicular cancer related to mobile phone use.

Meta-analyses and reviews

Two meta-analyses of mobile phone use and brain tumours have been published, both showing a small but statistically significant increase in risk associated with mobile phone use for at least 10 years. Kan and co-workers [Kan, et al. 2008] compiled the results from nine case-control studies of mobile phone use and brain tumours. The analysis included only studies published since 2000, but the rationale for this limitation was unclear. An increased risk of any brain tumour associated with 10 or more years of use was found based on five studies. Subgroup analyses e.g. by duration of use or network type were conducted only for all tumour types combined, not by histological type. No results were shown by laterality or amount of use. It is unclear if overlap between published studies was taken into account. The study by Hardell [Hardell, et al. 2002] was not included in the analysis due to insufficient reporting, nor was the earlier Hardell report as it was published prior to 2000 [Hardell, et al. 1999]. For some reason, studies by Muscat and Takebayashi on acoustic neurinoma were not mentioned [Muscat, et al. 2002; Takebayashi, et al. 2006], most likely because they were not retrieved by the literature search.

Hardell et al. also published a pooled analysis of epidemiological studies on mobile phone use and brain tumours [Hardell, et al. 2007b]. Though not specified in the report, it appears that studies published by the end of 2006 were included. Random effects model was used, though heterogeneity analyses were not shown. Non-significant association with mobile phone use ≥10 years was found for glioma (six studies), meningioma (four studies) and acoustic neuroma (four studies). For ipsilateral use for at least 10 years, a significantly increased risk was found for glioma and acoustic neuroma, with borderline significance for meningioma. No estimates for contralateral use were given and were not even discussed, though it might help interpretation of the results related to ipsilateral use (possible bias related to recall of side of use). The studies included in the analysis are described in detail, but sometimes incorrectly e.g. the description of the first Hardell study [Hardell, et al. 1999] as hospital-based. The meta-analysis itself is described only very briefly. For instance, the number of cases and controls on which the pooled estimates were based are not explicitly reported. Statistical methods used in pooling are also partly unclear. For instance, it is not reported if the analyses are based on case and control frequencies or adjusted OR's. It is not clear if the overlap between some of the studies was taken into consideration. No analysis by amount of phone use e.g. duration of calls was conducted, probably due to lack of consistent grouping between studies. In meta-analyses, comprehensive coverage is a key principle. Therefore it is a major weakness that selection of studies for pooling appears arbitrary. E.g. justification for the exclusion of the Danish cohort study is vague and does not seem to represent a priori defined quality criteria. It is also unclear why the NCI case-control study [Inskip, et al. 2001] is not included in the laterality analysis. It appears that studies with maximal duration of exposure less than 10 years were excluded.

Meta-analyses summarize the results of published studies. This adds precision, but is subject to similar biases as original reports, because pooling does not reduce systematic error. The results indicate a possible risk associated with long-term use, which needs to be interpreted with caution, bearing in mind the possible recall bias, selection bias and other uncertainties.

Exposure assessment

In an analysis comparing data from the Danish cohort study and the Danish Interphone study, agreement between self-reported mobile phone use and operator records was assessed [Schuz and Johansen 2007]. The material consisted of 533 cases and 822 controls, who had reported being mobile phone users already in 1982-95. The findings indicate a moderate agreement (kappa 0.3) between the two sources of information. The authors regard self-reports as the golden standard, but it appears that both sources of information are likely to be inaccurate.

Morrissey recruited volunteers (number not reported) among Motorola employees in the US, Europe and Malaysia [Morrissey 2007]. Output power during mobile phone use was recorded at 2.5 s intervals by a software modified GSM triband phone during a two week period. The findings indicate lower average power, but higher peak power in Europe compared with the US. This was attributable to the dual band operations (900/1800 MHz in Europe) in contrast to single band (1900 MHz in the US). Further, substantial variability (by up to 2-3 orders of magnitude) between calls was noted even for a single individual for calls within the same area.

Hillert assessed variation in power output in different circumstances in Sweden and the UK [Hillert, et al. 2006]. The measurements were conducted using 900/1800 MHz GSM phones, with proportion of time on maximal power (2 W) as the outcome. The unit of observation was a single call rather than a user. The main finding was that the power output was higher in rural than urban areas (around 50% versus less than 15% in Sweden, with even greater difference in the UK). Other features (use while moving vs. stationary, indoor vs. outdoor environment, length of call) did not affect the power substantially. The findings are consistent with the earlier Swedish report by Lönn et al. [Lonn, et al. 2004] though they differ from studies in some other countries.

In a study of mobile phone output power with 53 volunteers, the strongest determinant of power during a 5-day period was area (New York City vs. New Jersey vs. San Francisco), followed by stationary/moving and indoor/outdoor [Erdreich, et al. 2007]. These factors, however, explained only 11% of the variance. Yet, amount of variance explained is not a good indicator of the performance of a measure, other metrics e.g. area under the curve of a receiver-operating characteristic would be preferable. These results differ from those found in Sweden and Italy, which shows the lack of consistency and difficulty of constructing widely applicable proxy indicators for power and SAR.

These results taken together emphasize the substantial variability in RF exposure related to mobile phone use. It appears that an algorithm to accurately capture the variation in power levels and SAR would be exceedingly difficult to construct. This is likely to induce non-differential misclassification, which should be taken into account when interpreting the results of epidemiological studies.

As part of the Interphone study, Vrijheid et al. performed a validation study of short term recall of mobile phone use [Vrijheid, et al. 2006]. A convenience sample of 672 healthy volunteers in 11 countries was enrolled in the study. Actual mobile phone use was recorded by operators during a period varying between 3 – 8 months, or through software modified phones used during one month. Six to 12 months later the subjects were asked to recall the number and duration of mobile phone calls. Number of calls was generally underestimated; the ratio of geometric means of actual vs recalled number of calls was 0.92 (95% CI 0.85-0.99), and varied between countries from 0.42 to 1.61; an overestimation of number of calls was found in 4 countries. Of the subjects, 57% under- or overes-

timated their number of calls by less than a factor of 2. The ratio of recalled to actual duration of calls was larger on average than that for number of calls. Duration of calls was overestimated in all but two countries (geometric mean ratio overall=1.42; 95% CI 1.29-1.56), and varied between countries from 0.56 to 2.47. Only 42% of subjects over- or underestimated their duration of use by less than a factor of 2. The ratio of recalled to actual duration of calls increased with increasing duration of phone use; this pattern was seen in all but two countries. The same tendency was seen for recall of number of calls. There was a substantial individual variation in recall of both number and duration of calls. This study indicates that estimates of mobile phone use based on self-reported retrospective information are subject to substantial random errors, and that errors in duration of calls is greater than for number of calls. There seem to be a tendency for light users to underestimate their use, whereas heavy users tend to overestimate their use. The study is limited by the restriction to short term recall in healthy volunteers, but results indicate that exposure misclassification can lead to a dilution of risk estimates, should there be a true effect of mobile phone use on cancer risk. To evaluate effects of recall bias, a validation study would need to include information from cancer cases and controls, and retrospective exposure information that covers a longer duration.

Occupational studies

The effects of occupational exposure to radiofrequency EMF on brain tumours were assessed in the German Interphone study. The material consisted of 381 meningioma and 366 glioma cases with 1494 controls [Berg, et al. 2006]. The response proportion was 84% among cases and 63% among controls. Exposure assessment was based on interviews with assessment of specific tasks. No obvious association between brain tumour risk and occupational RF exposure was found (OR related to highest exposure 1.2 for glioma (0.7-2.2) and 1.3 (0.6-3.0) for meningioma based on 22 exposed glioma and 11 meningioma cases). The results are consistent with earlier studies and the main limitation was due to the small number of exposed cases (and lack of measurements in the development of exposure estimates).

Another study of occupational RF exposure on glioma risk was conducted in Australia [Karipidis, et al. 2007]. Exposure was estimated based on occupational history and a job-exposure matrix constructed in Finland. Only 18 cases were classified as exposed and no increased risks could be shown. In an alternative analysis, self-reported exposure and expert assessment were used, with largely comparable findings. Results for ELF were also negative.

A large Norwegian study evaluated the relationship between paternal occupational exposure to RF fields and adverse pregnancy outcome [Mjoen, et al. 2006]. Information on pregnancy outcome was obtained from the Medical Birth Registry. Information on occupation was obtained from census and an expert panel constructed an exposure classification (possible and probable exposure) based on job title. Of all the 1.1 million births during 1976-1995, roughly 540,000 (49%) had information on paternal identity and occupation available. No increased risks of congenital malformations were observed. A slightly increased risk of pre-term delivery was found (OR=1.08, 1.01.15). The limitations of the study are typical for registry-based research i.e. lack of exposure measurements and information on other exposure. The strengths include large sample size and comprehensive, non-selective outcome information available, although the power to study specific types of malformations was limited.

Symptoms near base stations or from other environmental exposures

Preece et al. assessed symptoms and health-related quality of life in two villages close to military antenna and one unexposed village in Cyprus [Preece, et al. 2007]. Spot measurements at a few places in each village using Delta-T multichannel loggers and portable Narda EMR 20C meter showed higher field strengths for the exposed villages than control area (average readings 0.5-0.6 Vm^{-1} versus <0.01 Vm^{-1}), even if the contribution of the frequencies used by the military antennae (17.6 MHz) was only 10-20%. A cross-sectional survey was carried out and it showed higher prevalence of headache and dizziness in the exposed villages. Health-related quality of life was also poorer in the exposed villages. Residents in the exposed villages had also the highest risk perception across a wide range of risks, many of which were unrelated to electromagnetic fields. Questionnaires were distributed to households rather than individuals, and the numbers of participating subjects were not given. It is unclear whether reported response proportions refer to households or individuals. Other characteristics of the different villages were not given, such as level of urbanization, type of buildings, age and sex distribution. There were significant differences in educational level between villages. The cross-sectional design, and the lack of individual data on exposure levels and potential confounders makes it impossible to draw any conclusions regarding the effect of RF exposure on studied health outcomes.

Concluding remarks on epidemiological RF studies

Few new data on mobile phone use and brain tumour risk have been published during the last year. The two national Interphone publications are based on very small numbers and do not change the overall assessment. The two published meta-analyses provide little additional information. Validation studies indicate that there may be substantial recall errors in self-reported mobile phone use, which needs to be taken into consideration in the interpretation of studies of mobile phone use, and studies on exposure assessment emphasize substantial variability in output power of mobile phones, which indicates heterogeneity in field strength in different usage circumstances.. Recent studies of occupational exposures have generally been too small, or registry based with crude exposure assessment and lack of information on potential confounders. The study of RF exposure from military antenna has limitations that preclude conclusions about potential effects of RF exposure.

Extrapolation to new signals

In EMF experimental investigations, animal and cellular models are used to assess the potential human health effects caused by exposure to the fields. There is thus a need to extrapolate the knowledge so acquired to the human and this adds to uncertainty.

What is particularly considered here is the extrapolation of the data obtained using one particular type of EMF signal to another signal. Most of the recent research on RF electromagnetic fields has dealt with mobile telephony, with its successive generations (e.g., NMT, GSM, UMTS). Extrapolation between these various types of signals is not straightforward because of their different time profiles (different modulations, existence of pulses). The task is becoming more and more complex in view of the facts that:

- the variety of signals as well as the usage (body-worn devices) is increasing,

- the existence of nonthermal effects of RF fields is still uncertain, in particular regarding long-term exposure, in spite of 20 years of active research,
- there is no definite conclusion about the role of modulation in inducing or modifying the biological effects,
- the metric for the absorbed "dose" has not been agreed upon: the SAR (local or whole-body) is presently the most commonly used in standard setting in particular, but others are being considered, such as temperature elevation.

Research is needed to explore how data obtained on past and current mobile telephony signals can be used for new (UMTS) and emerging (UWB) signals without performing again batteries of tests on biological models, which is a time-consuming and expensive process. A key issue is the possible existence of modulation-specific effects; extrapolation between different signals is substantially easier, if biological effects depend only on the amount of absorbed energy.

Extrapolation is also needed between cells and animals, animals and humans, adults and children, healthy and aged or sick subjects. This adds to the difficulty of the task, but it has to be performed as the various communication systems are being implemented rapidly and concerns being expressed widely about potential health effects.

Recently published reviews

Extremely low frequency fields environmental health risk assessment – WHO EHC document

This recent WHO Environmental Health Criteria (EHC) Document on ELF Fields (Doc No. 238, WHO, 2007), downloadable from the WHO EMF Project website (www.who.int/emf) [WHO 2007], addresses the possible health effects of exposure to extremely low frequency (ELF) electric and magnetic fields. It is a report from the WHO-appointed Task Group, which comprised 20 scientists from 16 different countries, and its main objectives are to review the scientific literature on the biological effects of exposure to ELF fields in order to assess any health risks from exposure to these fields and to use this health risk assessment to make recommendations to national authorities on health protection programs. The advice from WHO stemming from this document is contained in an ELF Fact Sheet No 322, available from the same website.

The frequencies under consideration range from above 0 Hz to 100 kHz. By far the majority of studies have been conducted on power-frequency (50 or 60 Hz) magnetic fields, with a few studies using power-frequency electric fields. In addition, there have been a number of studies concerning very low frequency (VLF, 3–30 kHz) fields, switched gradient magnetic fields used in magnetic resonance imaging, and the weaker VLF fields emitted by visual display units and televisions.

The health risk assessments carried out by WHO encompass four distinct steps: *hazard identification*, which is a qualitative evaluation of the weight of evidence in the scientific literature of adverse health effects resulting from ELF field exposure; *exposure assessment* for various occupational, environmental and domestic situations; *exposure-response assessment*, which comprises a quantitative evaluation of the relationship between exposure and likely resultant incidence of adverse health effects; and finally *risk characterization*, which provides estimates of the risk to human health under relevant exposure sce-

narios. The ELF health risk assessment described here was used in the development of appropriate public health measures for the management of ELF field risks and to make recommendations for further research.

Hazard identification

It is worth noting at the outset that, according to the WHO Constitution, health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. An adverse health effect is therefore a detrimental change in the complete physical, mental and/or social wellbeing of an individual or a number of individuals. In the evaluation of human health risks, sound human data, whenever available, are generally more informative than animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies; a detailed review of the conclusions regarding these data is not included here.

The review of scientific literature carried out for hazard identification of a given health outcome used terms based on IARC classification of the strength of evidence for cancer. Evidence is termed "limited" when it is restricted to a single study or when there are unresolved questions concerning the design, conduct or interpretation of a number of studies. "Inadequate" evidence is used when the studies cannot be interpreted as showing either the presence or absence of an effect because of major qualitative or quantitative limitations, or when no data are available.

The conclusions of the Task Group regarding hazard identification are, in summary, as follows:

Cancer

The IARC classification of ELF magnetic fields as "possibly carcinogenic to humans" [IARC 2002] was based upon all of the available data prior to and including 2001. The review of literature on cancer in the EHC monograph focuses mainly on studies published after the IARC review. The IARC classification was heavily influenced by the associations observed in epidemiological studies on childhood leukaemia. The Task Group considered that the classification of this evidence as limited does not change with the addition of two childhood leukaemia studies published after 2002. Since the publication of the IARC monograph the evidence for other childhood cancers remains inadequate.

Subsequent to the IARC monograph a number of reports have been published concerning the risk of female breast cancer in adults associated with ELF magnetic field exposure. These studies are larger than the previous ones and less susceptible to bias, and overall negative. With these studies, the evidence for an association between ELF magnetic field exposure and the risk of female breast cancer is weakened considerably and does not support an association with breast cancer.

With regard to the evidence from animal and *in vitro* laboratory studies, most of the data are negative. Three independent large-scale studies of rats provided no evidence of an effect of ELF magnetic fields on the incidence of spontaneous mammary tumours. Most studies report no effect of ELF magnetic fields on leukaemia or lymphoma in rodent models. Several large-scale long-term studies in rodents have not shown consistent increase in any type of cancer, including haematopoietic, mammary, brain and skin tumours. The Task Group acknowledged however that there is currently no adequate animal model of the most common form of childhood leukaemia, acute lymphoblastic leukaemia.

Otherwise, the evidence that ELF magnetic field exposure can enhance tumour development in combination with carcinogens is considered inadequate.

Generally, studies of the effects of ELF field exposure of cells have shown no induction of genotoxicity at fields below 50 mT. The notable exception is evidence from recent studies reporting DNA damage at field strengths as low as 35 μT; however, these studies are still being evaluated and our understanding of these findings is incomplete. There is also increasing evidence that ELF magnetic fields may interact with DNA-damaging agents. There is no clear evidence of the activation by ELF magnetic fields of genes associated with the control of the cell cycle. However, systematic studies analysing the response of the whole genome have yet to be performed. Many other cellular studies, for example on cell proliferation, apoptosis, calcium signalling and malignant transformation, have produced inconsistent or inconclusive results.

The overall conclusion regarding cancer is that the new human, animal and *in vitro* studies, published since the IARC [2002] monograph, do not change the overall classification of ELF magnetic fields as a possible human carcinogen.

Reproductive and developmental disorders

On the whole, epidemiological studies have not shown an association between adverse human reproductive outcomes and maternal or paternal exposure to ELF fields. There is some evidence for an increased risk of miscarriage associated with maternal magnetic field exposure, but this evidence is inadequate.

Overall, the evidence for developmental and reproductive effects in human and animal studies is inadequate.

Cardiovascular disorders

Experimental studies of both short-term and long-term exposure indicate that while electric shock is an obvious health hazard, other hazardous cardiovascular effects associated with ELF fields are unlikely to occur at exposure levels commonly encountered environmentally or occupationally.

Although various cardiovascular changes have been reported in the literature, the majority of effects are small and the results have not been consistent within and between studies. After an initially positive study of utility workers, follow-up studies of cardiovascular disease morbidity and mortality has not shown an association with exposure. Whether a specific association exists between exposure and altered autonomic control of the heart also remains speculative. Overall, the evidence does not support an association between ELF exposure and cardiovascular disease.

Neurodegenerative disorders

It has been hypothesized that exposure to ELF fields is associated with several neurodegenerative diseases. For Parkinson's disease and multiple sclerosis the number of studies has been small and there is no evidence for an association with these diseases. For Alzheimer's disease and amyotrophic lateral sclerosis (ALS) more studies have been published. Some of these reports suggest that people employed in electrical occupations might have an increased risk of ALS. So far, no biological mechanism has been established which can explain this association, although it has been suggested that it could have arisen because of electric shocks. Overall, the evidence for the association between ELF exposure and ALS is considered to be inadequate.

The few studies investigating the association between ELF exposure and Alzheimer's disease are inconsistent. However, the higher quality studies that focused on Alzheimer morbidity rather than mortality do not indicate an association. Altogether, the evidence for an association between ELF exposure and Alzheimer's disease is inadequate.

Neurobehavioral effects

Exposure to power-frequency electric fields causes well-defined biological responses, ranging from perception to annoyance, through surface electric charge effects. These responses depend on the field strength, the ambient environmental conditions and individual sensitivity. Thresholds for the discharge from a charged object through a grounded person depend on the size of the object and therefore require specific assessment.

High field strength, rapidly pulsed magnetic fields can stimulate peripheral or central nerve tissue; such effects can arise during magnetic resonance imaging (MRI) procedures, and are used in transcranial magnetic stimulation. The function of the retina, which is a part of the CNS, can be affected by exposure to much weaker ELF magnetic fields than those that cause direct nerve stimulation; a flickering light sensation (magnetophosphenes) results from the interaction of the induced electric field with electrically excitable retinal cells.

The evidence for other neurobehavioural effects in volunteer studies, such as the effects on brain electrical activity, cognition, sleep, hypersensitivity and mood, is less clear. Generally, such studies have been carried out at exposure levels below those required to induce the effects described above, and have produced evidence only of subtle and transitory effects at best. It is possible that these inconsistencies may be attributable in part to differences in the design of the studies.

Some people claim to be hypersensitive to EMFs in general. However, the evidence from double-blind provocation studies suggests that the reported symptoms are unrelated to short term EMF exposure in the laboratory.

There are only few studies of depressive symptoms or suicide; they are inconsistent and inconclusive. Thus, this evidence is considered inadequate.

Neuroendocrine system responses

The results of volunteer studies as well as residential and occupational epidemiological studies suggest that the neuroendocrine system is not adversely affected by exposure to power-frequency electric or magnetic fields. This applies particularly to the circulating levels of specific hormones of the neuroendocrine system, including melatonin, released by the pineal gland, and to a number of hormones involved in the control of body metabolism and physiology, released by the pituitary gland. Most laboratory studies of the effects of ELF exposure on night-time melatonin levels in volunteers found no effect when care was taken to control possible confounding.

Overall, the human, animal and *in vitro* data do not indicate that ELF electric and/or magnetic fields affect the neuroendocrine system in a way that would have an adverse impact on human health and the evidence is thus considered inadequate.

Immunological and haematological responses

Evidence for the effects of ELF electric or magnetic fields on components of the immune system is generally inconsistent. Many of the cell populations and functional markers

were unaffected by exposure. However, in some human studies, changes were observed in natural killer cells, which showed both increased and decreased cell numbers, and in total white blood cell counts, which showed no change or decreased numbers. The difficulty in interpreting the potential health impact of these data is due to the large variations in exposure and environmental conditions, the relatively small numbers of subjects tested and the broad range of endpoints.

There have been few studies carried out on the effects of ELF magnetic fields on the haematological system and no consistent effects have been found in either human or animal studies.

Overall therefore, the evidence for effects of ELF electric or magnetic fields on the immune and haematological system is considered inadequate.

Overall hazard identification

ELF electric and magnetic fields can affect the nervous systems of people exposed to them, resulting in adverse health consequences such as nerve stimulation, at very high exposure levels. Exposure at lower levels induces changes in the excitability of nervous tissue in the central nervous system which may affect memory, cognition and other brain functions. These acute effects on the nervous system form the basis of international guidelines. However, they are unlikely to occur at the low exposure levels in the general environment and most working environments.

Exposure to ELF electric fields also induces a surface electric charge which can lead to perceptible, but non-hazardous effects, including microshocks.

Scientific evidence suggesting that everyday, chronic, low-intensity ELF magnetic field exposure poses a possible health risk is based on epidemiological studies demonstrating a consistent pattern of an increased risk of childhood leukaemia. However, virtually all of the laboratory evidence and the mechanistic evidence fail to support a relationship between low-level ELF magnetic field exposure and changes in biological function or disease status. Thus, on balance, the evidence relating to childhood leukaemia is not strong enough to be considered causal and therefore ELF magnetic fields remain classified as possibly carcinogenic.

A number of other diseases have been investigated for possible association with ELF magnetic field exposure. These include other types of cancers in children and adults, depression, suicide, reproductive dysfunction, developmental disorders, immunological modifications, neurological disease and cardiovascular disease. The scientific evidence supporting a linkage between exposure to ELF magnetic fields and any of these diseases is weaker than for childhood leukaemia and in some cases (for example, for cardiovascular disease or breast cancer) the evidence is sufficient to give confidence that magnetic fields do not cause the disease.

Exposure assessment

Electric and magnetic fields exist wherever electricity is generated, transmitted or distributed in power lines or cables, or used in electrical appliances. Since the use of electricity is an integral part of our modern lifestyle, these fields are ubiquitous in our environment.

Residential exposures

In the case of residential exposure, data from various countries show that the geometric means of ELF magnetic field strengths across homes do not vary dramatically. Mean values of ELF electric fields in the home can be up to several tens of volts per metre. In the vicinity of some appliances, the instantaneous magnetic field values can be as much as a few hundreds of microtesla. Close to power lines, magnetic fields reach as much as approximately 20 μT and electric fields can be between several hundreds and several thousands of volts per metre.

The epidemiological studies on childhood leukaemia have focused on average residential ELF magnetic fields above 0.3 to 0.4 μT as a risk factor for cancer. Results from several extensive surveys showed that approximately 0.5–7% of children had time-averaged exposures in excess of 0.3 μT and 0.4-3.3% were exposed to in excess of 0.4 μT. Calculations based on case-control studies of ELF magnetic field exposure and childhood leukaemia resulted in similar ranges.

Occupational exposure

Occupational exposure, although predominantly to power-frequency fields, may also include contributions from other frequencies. The average magnetic field exposures in the workplace have been found to be higher in "electrical occupations" than in other occupations such as office work, ranging from 0.4–0.6 μT for electricians and electrical engineers to approximately 1 μT for power line workers, with the highest exposures for welders, railway engine drivers and sewing machine operators (above 3 μT). The maximum magnetic field exposures in the workplace can reach approximately 10 mT and this is invariably associated with the presence of conductors carrying high currents. In the electrical supply industry, workers may be exposed to electric fields up to 30 kV m^{-1}.

Exposure-response assessment

Frequency-dependent thresholds have been identified for acute adverse health effects on electrically excitable tissues, particularly those in the central nervous system. These effects result from electric fields and currents that are induced in body tissues by ELF electric or magnetic field exposure. There will be a certain amount of imprecision in determining these thresholds; the degree of uncertainty is reflected partly in the safety factors incorporated into exposure limits.

In the epidemiological studies on childhood leukaemia the risk is only seen above 0.3 to 0.4 μT of average residential ELF magnetic fields. However, there is a large amount of misclassification in these data consistent with a variety of dose-response patterns relating chronic adverse health effects and magnetic field exposure.

Risk characterisation

Exposure limits based on the acute effects on electrically excitable tissues, particularly those in the CNS, have been proposed by several international organizations. Acute adverse health effects will be avoided if exposures are restricted to levels below the guidelines.

With regard to possible long term health effects, the most common means of characterizing risks from epidemiological data for a single endpoint is to use the attributable fraction, which is the proportion of cases of a disease that is attributable to the exposure. However, the assumption of a causal relationship is critical to this evaluation. Although a causal relationship between magnetic field exposure and childhood leukaemia has not

been established, the possible public health impact has been calculated assuming causality in order to provide a potentially useful input into policy. However, these calculations are highly dependent on the exposure distributions and other assumptions, and are therefore very imprecise. Assuming that the association is causal, the number of cases of childhood leukaemia worldwide that might be attributable to exposure was estimated to range from 100 to 2400 cases per year. This represents 0.2 to 4.9% of the total annual incidence of leukaemia cases, estimated to be 49,000 worldwide in 2000 AD. Thus, in a global context, the impact on public health, if any, would be limited and uncertain.

There are a number of other sources of uncertainty in the risk calculation apart from those directly involved in the calculation of attributable fractions. In particular, the consistently observed association between average magnetic field exposure and childhood leukaemia might be due to selection bias which might be present in some of the studies. However, selection bias was considered unlikely to fully account for the observed relationship. Misclassification while present is likely to reduce the observed association. A search for other factors which can potentially confound the association has not been fruitful.

Moreover, if the effect was real, then it is not known what exposure metric would define this relationship, nor what interaction mechanism could explain it. With regard to the latter, three stand out as potentially operating at lower field levels than the others: induced electric fields in neural networks, radical pairs and magnetite.

Protective measures

It was concluded that it is essential that exposure limits be implemented in order to protect against the established adverse acute effects of exposure to ELF electric and magnetic fields.

The uncertainties about the existence of chronic effects, indicated by the limited evidence for a link between exposure to ELF magnetic fields and childhood leukaemia suggests that implementing suitable precautionary procedures to reduce exposure is reasonable and warranted. However, these precautionary approaches should not compromise the obvious health, social and economic benefits brought by electric power. Furthermore, given both the weakness of the evidence for a link between exposure to ELF magnetic fields and childhood leukaemia, and the limited impact on public health if there is a link, the benefits for health of exposure reduction are unclear. Thus it was considered that the costs of precautionary measures should be very low.

Various recommendations include the implementation of very low cost measures, to reduce exposure, in the construction of new facilities and appliances. The Task Group also recommended the implementation of effective and open communication strategies with stakeholders and the improved planning of ELF-emitting facilities.

WHO-EHC Task Group recommendations for research

Finally, the Task Group recommended that governments and industry should promote research programmes in order to reduce scientific uncertainty and made a number of specific research proposals, particularly in relation to childhood leukaemia. Those considered a high priority are summarised below:

It was concluded that there were no substantive health issues related to ELF electric fields at levels generally encountered by members of the public. Thus, further research recommendations concern the possible acute and long term effects of exposure to ELF magnetic fields.

With regard to epidemiological studies, it was considered that a high priority should be given to: a) updating the pooled analyses of childhood leukaemia with information from new studies; b) conducting a pooled analysis of childhood brain cancer studies, since this can inexpensively provide greater and improved insight into existing data; and c) further investigation of the association between amyotrophic lateral sclerosis and 'electric occupations', since it is considered important to find out whether ELF magnetic fields, electric shocks, or both are involved in the causation of this rare neurodegenerative disease.

For animal studies, it was considered that resolving the conflict between epidemiological results and experimental and mechanistic results for childhood leukaemia is the highest priority. To this end, the development of transgenic mouse models for childhood leukaemia should be undertaken in order to provide appropriate experimental animal models relevant to the epidemiological data showing an association of EMF exposure with childhood leukaemia. It was also considered that high priority should be given to animal and *in vitro* studies in which ELF fields are rigorously evaluated as a co-carcinogen.

With regard to biophysical interaction mechanisms, it was recommended that the extent to which multi-cell mechanisms such as neural networks operate in the body, to improve signal-to-noise ratios should be further investigated. In addition, further investigation of the threshold and frequency response of the neuronal networks in the hippocampus and other parts of the brain should be examined using *in vitro* approaches.

The identification of gaps in knowledge about occupational ELF exposure, such as in MRI, was considered a high priority research need.

Finally, it was recognised that the development of adequate health protection policies for communities and the communication of appropriate information concerning risk form an important part of the way in which developing technologies are integrated into society. Although the following were not given a high priority, it was recommended that a cost-benefit/effectiveness analysis for mitigation of ELF magnetic fields should be developed. In addition, it was thought that further research should be conducted on: a) risk perception and communication focused on ELF magnetic fields; b) the development and implementation of health protection policies in areas of scientific uncertainty.

SCENIHR on EMF

The European Commission Scientific Committee on Newly Identified Health Risks [SCENIHR 2007] had been asked to update the previous opinion from 2001. In preparation for this update, scientific data published since the previous opinion has been reviewed and their impact on the conclusions of the previous opinion has been assessed. The present opinion is divided according to frequency band. A separate section discusses environmental effects.

Radio frequency fields (RF fields)

Since the adoption of the 2001 opinion extensive research has been conducted regarding possible health effects of exposure to low intensity RF fields, including epidemiologic, in vivo, and in vitro research.

The balance of epidemiologic evidence indicates that mobile phone use of less than 10 years does not pose any increased risk of brain tumour or acoustic neuroma. For long-term use, data are sparse, and the following conclusions are therefore uncertain and tentative. However, from the available data it does appear that there is no increased risk for

brain tumours in long-term users, with the exception of acoustic neuroma for which there is some evidence of an association. For diseases other than cancer, very little epidemiologic data are available.

A particular consideration is mobile phone use by children. While no specific evidence exists, children or adolescents may be more sensitive to RF field exposure than adults. Children of today will also experience a much higher cumulative exposure than previous generations. To date no epidemiologic studies on children are available.

Observational and provocation studies have failed to provide consistent support for a relation between RF exposure and self-reported symptoms (sometimes referred to as electromagnetic hypersensitivity).

Studies on neurological effects and reproductive effects have not indicated any health risks at exposure levels below the ICNIRP-limits established in 1998.

Animal studies have not provided evidence that RF fields could induce cancer, enhance the effects of known carcinogens, or accelerate the development of transplanted tumours. The open questions include adequacy of the experimental models used and scarcity of data at high exposure levels.

There is no consistent indication from in vitro research that RF fields affect cells at the non-thermal exposure level.

The technical development is very fast and sources of RF field exposure become increasingly common. Yet, there is a lack of information on individual RF field exposure and the relative contribution of different sources to the overall exposure.

In conclusion, no health effect has been consistently demonstrated at exposure levels below the ICNIRP-limits established in 1998. However, the data base for this evaluation is limited especially for long-term low-level exposure.

Intermediate frequency fields (IF fields)

Experimental and epidemiological data from the IF range are very sparse. Therefore, assessment of acute health risks in the IF range is currently based on known hazards at lower frequencies and higher frequencies. Proper evaluation and assessment of possible health effects from long term exposure to IF fields are important because human exposure to such fields is increasing due to new and emerging technologies.

Extremely low frequency fields (ELF fields)

The previous conclusion that ELF magnetic fields are possibly carcinogenic, chiefly based on childhood leukaemia results, is still valid. There is no generally accepted mechanism to explain how ELF magnetic field exposure may cause leukaemia.

The calculations in the previous opinion of the possible proportion of childhood leukaemia cases that might be attributed to ELF fields still hold.

For breast cancer and cardiovascular disease, recent research has indicated that an association is unlikely. For neurodegenerative diseases and brain tumours, the link to ELF fields remains uncertain. A relation between ELF fields and symptoms (sometimes referred to as electromagnetic hypersensitivity) has not been demonstrated.

Static fields

Adequate data for proper risk assessment of static magnetic fields are very sparse. Developments of technologies involving static magnetic fields, e.g. with MRI equipment require risk assessments to be made in relation to the exposure of personnel.

Environmental effects

The continued lack of good quality data in relevant species means that there is insufficient data to identify whether a single exposure standard is appropriate to protect all environmental species from EMF. Similarly the data is inadequate to judge whether the environmental standards should be the same or significantly different from those appropriate to protect human health.

Important research needs were identified within all frequency bands.

The UK Stakeholder Advisory Group on ELF EMF (SAGE) report

The UK Stakeholder Advisory Group on ELF EMF (SAGE) issued its First Assessment on precautionary approaches to EMF from high-voltage overhead power lines, residential wiring, and appliances [SAGE Report 2007]. The 40-member stakeholder advisory group came from government and health agencies, academia, the electricity industry, local and national individuals/campaigners and other industries and groups. Two distinctly different points of view about the strength of evidence for health endpoints other than childhood leukaemia were held by the stakeholders, so consensus was not reached on how to advise the UK government. Thus, there are two alternative SAGE recommendations on power lines, and SAGE urged the Government to make a clear choice.

One view about the strength of evidence approach they call the "WHO/HPA" view, the other is called the "California" view. Both views acknowledge a consistent statistical association (which may or may not reflect causation) exists in epidemiological studies between unusually high background magnetic fields found in homes and a raised risk for childhood leukaemia. However, the WHO/HPA view is that only for childhood leukaemia is the evidence sufficiently strong to form the basis of precautionary actions. With the evidence for other adverse health effects as too weak to justify precautionary measures with significant costs. Alternatively, the 'California' view identifies some other health effects as sufficiently strong to form the basis of precautionary actions. While acknowledging that there is less agreement about whether these health effects might be caused by power lines, the public health consequences if they are would be considerably greater. On this basis, the costs and benefits of this option are considered to be at least comparable

Thus the group made two alternative recommendations to the Government depending on the different views. SAGE members did all agree to recommend that the UK government adopt two basic precautionary measures: provide better information for the public and use optimal phasing of 132-kV overhead lines not already thus phased. Additional low-cost precautionary options include fixing faulty wiring in homes. But because these would "not have a dramatic effect on exposures", some members identified a further option: restrict construction of new homes and schools in corridors near transmission lines. The report summarizes that if adopted, the corridor option would "probably be implemented as policy guidance rather than regulation" and that the main consequences of the corridor option would be as loss of land use and value.

Update on key issues

Based on current and previous reports it is now possible to assess the evidence for some key issues.

a. The possibility that some individuals are particularly sensitive and react with symptoms to exposure to EMF has been discussed in a previous report and also at a WHO workshop (WHO International Seminar and Working Group Meeting on EMF Hypersensitivity, http://www.who.int/peh-emf/meetings/hypersensitivity_prague2004/en/index.html). Additional studies were reviewed in the current report. While these symptoms are very real and some subjects suffer severely, there is hardly any evidence for EMF exposure being a causal factor.

b. The few studies that have been published on health risks among populations living near transmitters have had major methodological shortcomings. However, the exposure to the general population that results from transmitters is very weak and one would not expect such exposure to produce a health risk as discussed in the previous report. Indeed, one would assume that if RF exposure at low levels is associated with a health risk it would be considerably easier to detect it in studies of mobile phone users, or highly exposed occupational groups. The overall conclusion is that exposure from transmitters is unlikely to be a health risk.

c. Studies of cancer risk in mobile phone users have been discussed in all reports. Short-term use of mobile phones does not appear to be associated with brain or head and neck cancer risks in adults. However, other outcomes have not been studied, no studies on children or adolescents have been done, and long-term use has not been fully evaluated. In particular for acoustic neuroma there is a concern about long-term mobile phone use.

d. For power frequency fields the previous assessment by IARC remains unchanged, namely that ELF magnetic fields are a possible human carcinogen. WHO recommends in its ELF Environmental Health Criteria document (Doc No. 238, WHO, 2007) that implementing very low cost precautionary procedures to reduce exposure is reasonable and warranted.

e. High exposure to static magnetic fields occurs for example near MRI machines. Very little data exist for risk assessment related to long-term exposure to static fields. With regard to acute effects, it has become clear that movement in a static field of ~ 2 T or more might induce various sensations including vertigo and nausea, possibly related to the induction of electric fields and currents in the head. Individual sensitivity to such effects is variable.

f. Research on interaction mechanisms in both ELF and RF ranges below guideline levels is moderately active. The most plausible model for ELF (and static) field effects is magnetic field effect on radical pairs which may have seen some confirmation in some of the bird navigation investigations, but still at relatively high levels. There is no model yet for RF non-thermal mechanisms.

g. A biologically based hypothesis that magnetic fields increase the risk for cardiac arrhythmia-related conditions and acute myocardial infarction has been put forward. Currently available evidence, however, speaks against an etiologic relation between EMF exposure and cardiovascular disease.

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Comment on Lahkola et al. Int J Cancer 2007 (15 April, 2008)

Questions have been received why the Fifth Annual Report from SSI's Independent Expert Group on Electromagnetic Fields does not mention the paper by Lahkola et al. (Lahkola et al., Int. J. Cancer 2007). The Expert Group would like to comment that the paper was discussed by the group and was part of the basis for the conclusions. However, it was by mistake overlooked when preparing the report. The Expert Group regrets this accidental omission.

Prof. Anders Ahlbom,

Chairman, SSI's Independent Expert Group on Electromagnetic Fields

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STATENS STRÅLSKYDDSINSTITUT, SSI, är en central tillsynsmyndighet som verkar för ett gott strålskydd för människan och miljön, nu och i framtiden.

SSI sätter gränser för stråldoser till allmänheten och för dem som arbetar med strålning, utfärdar föreskrifter och kontrollerar att de efterlevs. SSI håller beredskap dygnet runt mot olyckor med strålning. Myndigheten informerar, utbildar och utfärdar råd och rekommendationer samt stöder och utvärderar forskning. SSI bedriver även internationellt utvecklingssamarbete.

Myndigheten, som sorterar under Miljödepartementet, har 110 anställda och är belägen i Solna.

THE SWEDISH RADIATION PROTECTION AUTHORITY (SSI) is a central regulatory authority charged with promoting effective radiation protection for people and the environment today and in the future.

SSI sets limits on radiation doses to the public and to those that work with radiation. SSI has staff on standby round the clock to respond to radiation accidents. Other roles include information, education, issuing advice and recommendations, and funding and evaluating research.

SSI is also involved in international development cooperation. SSI, with 110 employees located at Solna near Stockholm, reports to the Ministry of Environment.

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