SSI report

SSI Rapport
2007:04

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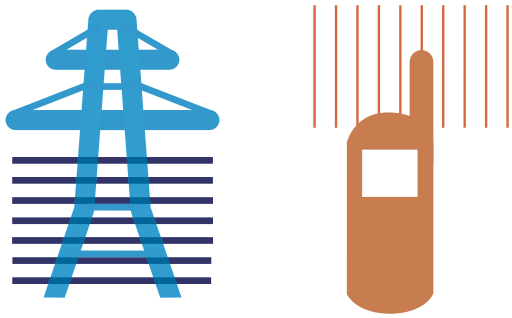
Recent Research on EMF and Health Risks

Fourth annual report from SSI's Independent Expert Group on Electromagnetic Fields, 2006



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.

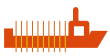
Health care
The second largest contribution to the total radiation dose to the Swedish population comes from health care. SSI is working to reduce the radiation dose to employees and patients through its regulations and its inspection activities.

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. Fourth annual report from SSI's Independent Expert Group on Electromagnetic Fields, 2006.

DEPARTMENT / AVDELNING: Department of Emergency Preparedness & Environmental Assessment / Avdelning för Beredskap och miljöövervakning.

SUMMARY: This year's report includes a preamble in which the work process of the group is described. In particular the methods for evaluation of the results of studies as well as for synthesizing the scientific evidence within a research area are described.

A recent childhood leukaemia study from Japan is in line with previous epidemiologic findings.

The effects of RF fields on many different genotoxicity endpoints have been evaluated both in vitro and in vivo using a wide range of exposure levels, and most of the studies have reported no effects. The most recent studies reviewed for the present report do not appear to strengthen the evidence of any genotoxic effects of RF fields. The results from the REFLEX project, reporting increased DNA strand breaks in cell cultures exposed to RF fields, need to be better understood before conclusions can be drawn.

A replication of the TNO study did not find effects of UMTS-like base-station RF radiation on cognitive performance and well-being.

Recently published studies on mobile phone use and cancer risk do not change the earlier overall assessment of the available evidence from epidemiological studies. In particular an extended follow up of a cohort study from Denmark does not alter the conclusions.

In the report for 2005 the expert group assessed the evidence for five key issues in health-related EMF research. In this years report the expert group has added one issue: Possible interaction mechanisms for weak exposure from ELF and RF electromagnetic fields.

SAMMANFATTNING: 2006 års rapport inleds med ett avsnitt där det vetenskapliga rådet förklarar hur man arbetar med att utvärdera vetenskapliga studier inom forskningsområdet elektromagnetiska fält och hälsa.

En japansk epidemiologisk studie av leukemi hos barn i relation till lågfrekventa magnetfält tyder på att ett samband finns och därmed stödjer den resultaten från tidigare forskning.

För radiofrekventa fält har ett antal olika studier genomförts för att undersöka eventuell genotoxicitet, både djurförsök och cellförsök, med olika exponeringar. Huvuddelen av dessa studier har inte sett några genotoxiska effekter. Några studier från det så kallade REFLEX-projektet (del i ett EU-program) indikerar dock att vissa effekter på DNA skulle kunna förekomma. Rådet menar emellertid att resultaten är svårtolkade och därför behövs bättre förståelse av resultaten och oberoende upprepningar innan slutsatser kan dras.

En upprepning av den så kallade TNO-undersökningen som rapporterade ökade symtom vid exponering av 3G-liknande signaler har inte funnit några samband med symtom och resultaten från TNO-studien har alltså inte kunnat upprepas.

Nya epidemiologiska studier om mobiltelefoni och cancer ändrar inte tidigare slutsatser. Det gäller även den nyligen publicerade uppföljningen av en kohortstudie från Danmark.

I förra årets rapport gjorde rådet sammanfattande bedömningar av det vetenskapliga underlaget för fem viktiga frågeställningar. Dessa bedömningar har inte ändrats på något avgörande sätt i årets rapport. Däremot uttalar sig rådet om ytterligare en frågeställning: Möjliga mekanismer för eventuella effekter av svag exponering för lågfrekventa och radiofrekventa elektromagnetiska fält.

Statens strålskyddsinstitut
Swedish Radiation Protection Authority

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Preface

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 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 forth annual report.

The composition of the group during 2006 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 2006

Anders Ahlbom

Chairman

Executive Summary

ELF (extremely low frequency) fields

Recent genotoxicity studies

The majority of previous animal and in vitro studies have found no evidence of genotoxicity of ELF magnetic fields at field strengths relevant to human exposure. The results of recent studies have not strengthened the evidence of genotoxic effects from ELF magnetic fields alone. However, there are suggestions that ELF magnetic fields might modify biological responses to other chemical and physical agents, although suggested mechanisms currently do not explain effects seen at exposure levels below 100 μT.

Mechanisms

The effects that form the basis of current exposure limits (excitation of nerves and muscles) require high fields (5000 μT or higher) and/or field gradients that rarely are likely to be present in the general environment (where average levels are below 1 μT).

Some mechanisms have been discussed as potentially operating at low exposure levels, e.g. narrow bandwidth mechanisms involving magnetic resonance phenomena and the "radical pair mechanism". The latter mechanism is currently probably the most plausible hypothesized mechanism. None of these mechanisms, however, is applicable at the exposure levels where effects on childhood leukaemia risk have been observed.

Recent epidemiological studies

A recent childhood leukaemia study is in line with previous epidemiologic findings. Another study on survival after childhood leukaemia diagnosis is a new approach and can be important both for understanding the development and treatment of childhood leukaemia, but needs replication. Neither of these results changes the overall IARC conclusions that ELF magnetic fields are 'possibly carcinogenic to humans'.

RF (radiofrequency) fields

Recent genotoxicity studies

The effects of RF fields on many different genotoxicity endpoints have been evaluated both in vitro and in vivo using a wide range of exposure levels, and most of the studies have reported no effects. The most recent studies reviewed for the present report do not appear to strengthen the evidence of any genotoxic effects of RF fields. The results from the REFLEX project, reporting increased DNA strand breaks in cell cultures exposed to RF fields, need to be better understood before conclusions can be drawn.

Human laboratory studies

Results from studies of mobile phone RF effects on cognitive function are inconsistent, but no single clear effect on cognitive function can be identified. In general, however, the many well-conducted studies that have been published recently do not confirm positive findings reported a few years ago in smaller, less methodically rigorous studies.

Most recent well-conducted studies of evoked or event-related potentials indicate a lack of effect of mobile phone RF radiation.

A replication of the TNO study did not find effects of UMTS-like base-station RF radiation on cognitive performance and well-being.

Differences between “RF-sensitive” and “non-sensitive” people can be seen in a number of physiological parameters that are strongly influenced by the autonomic nervous system, but these endpoints are not influenced by mobile phone RF radiation. In addition, people self-reporting as RF sensitive report experiencing headaches, nausea dizziness and other symptoms during mobile phone use at a very much greater prevalence than non-sensitive individuals. However, this is independent of whether the RF exposure is real or sham, and might reflect a conscious expectation of such effects.

Mechanisms

Current exposure guidelines are based on effects caused by heating of tissue (thermal effects). For exposures at levels generally regarded as “non-thermal” a few mechanisms for biological effects have been hypothesized. One hypothesis states that non-thermal RF effects ultimately are the result of thermo-receptor activation. These thermo-receptors are located on the surface as well as in many other parts of the body of warm-blooded animals, including the brain and the spinal cord.

Another hypothesis suggests that “demodulation” of the modulated-RF signals could occur. However, the only or most likely biological structure known to be non-linear and therefore able to demodulate, is the cell membrane which can demodulate only below approximately 1 MHz. Awaiting the outcome of an experiment aiming at detecting other nonlinear components of the cell, the consensus is still that demodulation is not biologically significant in the frequency range used for mobile telephony.

Recent epidemiological studies

Recently published studies on mobile phone use and cancer risk do not change the earlier overall assessment of the available evidence from epidemiological studies. In particular an extended follow up of a cohort study from Denmark does not alter the conclusions. Currently available evidence suggests that for adult brain tumours there is no association with mobile phone use for at least up to, say, ten years of use. For longer latency the majority of the evidence also speaks against an association, but the data are still sparse. The same conclusion holds for short-term use and acoustic neuroma. However, for long-term use and acoustic neuroma there is a concern, and more information is required. A study on symptoms near base stations did see an association between exposure level and prevalence of symptoms. These results need to be replicated and better understood before conclusions can be drawn.

Reviews

A recent review by the UK Independent Advisory Group on Non-ionising Radiation (AGNIR) concludes that the evidence to date does not support the hypothesis that exposure to power frequency EMFs affects melatonin levels or the risk of breast cancer.

Research priorities

Important research needs remain within all EMF frequencies as identified by the WHO EMF programme and more recently by EMF-NET and by SCENIHR (European Commission Scientific Committee). The Swedish Government has announced plans to provide an additional 10 million SEK for research administered by the SSI. Even though this funding will have to cover research within all areas of radiation protection, the SSI has pointed out EMF as a priority area. The IEG looks very positively at this and suggests that SSI specifies that a certain proportion of the available funds will indeed be used for EMF research.

Sammanfattning på svenska

Extremt lågfrekventa elektromagnetiska fält (ELF)

Genotoxicitet

Huvuddelen av tidigare djurförsök och cellförsök har inte funnit att ELF-fält har genotoxisk påverkan vid sådana fältstyrkor som befolkningen exponeras för. Aktuella studier har inte förändrat den bilden. Det finns dock indikationer på att ELF-fält skulle kunna ha biologisk påverkan tillsammans med andra kemiska eller fysikaliska exponeringar, men dessa resultat kan inte bidra till att förklara de resultat som ses vid exponeringar under 100 mikrotesla, dvs vid exponeringar som förekommer i den allmänna miljön.

Mekanismer

De effekter som ligger till grund för nu gällande riktvärden för ELF-magnetfält (nerv- och muskelretningar) utlöses bara vid fält av sådan styrka (5000 μT eller högre) att de ytterst sällan förekommer i den allmänna miljön (där nivåerna vanligtvis ligger under 1 μT). Det finns mekanismer som diskuterats och som potentiellt skulle kunna ha effekt vid låga exponeringsnivåer, t ex mekanismer vid smala bandbredder som involverar resonansfenomen och ”radical pair”-mekanismer. Den sistnämnda är troligen den för närvarande mest sannolika. Inte för någon av dessa har man dock kunnat påvisa att de har någon koppling till barnleukemirisk, som är den hälsoeffekt som har störst vetenskapligt stöd.

Epidemiologi

En nyligen publicerad studie av leukemi hos barn i relation till ELF-magnetfält tyder på att ett samband finns och stödjer därmed resultaten från tidigare forskning. En undersökning har studerat överlevnad hos barn med leukemi och relationen till ELF-magnetfält och funnit ett samband. Detta är en ny ansats och därmed av intresse även om storleken på denna studie var liten. Inget av dessa resultat påverkar slutsatsen i IARCs utvärdering, nämligen att ELF-magnetfält är ”possibly carcinogenic to humans”.

Radiofrekventa elektromagnetiska fält (RF)

Genotoxicitet

Ett antal olika genotoxistiska studier har genomförts både i djurförsök och i cellförsök och med olika exponeringar. Huvuddelen av dessa studier har inte sett några genotoxiska effekter. Resultaten från den så kallade REFLEX-studien (del i ett EU-program) indikerar dock att vissa effekter på DNA skulle kunna förekomma. Resultaten är dock svårtolkade och en bättre förståelse av utfallen och oberoende upprepningar krävs innan slutsatser kan dras.

Experimentella studier på människa

Resultaten från forskningen om kognitiva effekter är motsägelsefulla men ingen enskild tydlig effekt har kunna urskiljas. Många väl genomförda större studier har inte lyckats upprepa resultat från mindre studier som tidigare rapporterat samband. En upprepning av den så kallade TNO-undersökningen som rapporterade ökade symtom vid exponering av UMTS (3G)- lika signaler har inte funnit några samband med symtom och har alltså inte kunnat upprepa TNO-resultaten. Skillnader mellan ”RF-känsliga” personer och personer som inte är ”RF-känsliga” har påvisats i ett flertal studier bland annat på parametrar som är relaterade till det autonoma nervsystemet, men någon koppling till RF-exponering har inte kunnat ses. Personer som rapporterar sig vara ”RF-känsliga” har dessutom oftare symtom t ex huvudvärk, illamående, yrsel, än andra, men dubbelt blinda försök tyder på att förekomsten av dessa symtom är oberoende av exponering för RF-fält.

Mekanismer

Aktuella gränsvärden baseras på effekter från temperaturstegring. Det finns några hypoteser om effekter också vid lägre exponeringar, så kallade ”icke-termiska effekter”. En sådan hypotes innebär att effekter uppstår via aktivering av temperaturreceptorer som finns på många ställen i kroppen, även i hjärnan och ryggmärgen. En annan hypotes innebär att vissa RF-signaler demoduleras och därmed får en förstärkt påverkan till exempel på cellmembran.

Epidemiologi

Nyare epidemiologiska studier om mobiltelefoni och cancer ändrar inte tidigare slutsatser. Det gäller även den nyligen publicerade uppföljningen av en kohortstudie från Danmark. Baserat på det underlag som idag finns från epidemiologiska studier är bedömningen att det för hjärntumörer hos vuxna inte tycks finnas något samband med användning av mobiltelefon upp till omkring tio år. För längre tids användning talar också forskningen emot en sådan riskökning, men det finns än så länge bara ett fåtal studier tillgängliga. För tumörer i hörselnerven tycks inte heller korttidsanvändning av mobiltelefon ha något samband, men för längre tids användning finns en del data som tyder på att ett samband skulle kunna finnas. En undersökning av symtom hos en befolkning bosatt nära basstationer har visat på samband mellan symtom och exponering för RF-fält. Dessa resultat behöver upprepas i ytterligare studier innan slutsatser kan dras.

Rapporter

Storbritanniens oberoende forskningsråd för icke-joniserande strålning (AGNIR) publicerade nyligen en genomgång av forskningen om effekten av elektromagnetiska fält på melatonin och bröstcancer. Deras slutsats var att det idag inte finns något vetenskapligt stöd för att elektromagnetiska fält kan påverka melatoninnivåer eller bröstcancerrisk.

Forskningsbehov

WHOs EMF-program identifierar viktiga områden inom alla EMF-frekvenser där det finns behov av ytterligare forskning. Nyligen har även EMF-NET och SCENIHR (European Commission Scientific Committee) identifierat liknande forskningsbehov. Den svenska regeringen har offentliggjort planer på att tillskjuta ytterligare 10 miljoner till SSI

öronmärkt för forskning. Även om dessa resurser skall täcka forskning inom alla områden av strålskyddet har SSI pekat ut EMF som ett prioriterat område. SSIs vetenskapliga råd ser mycket positivt på detta och föreslår att SSI specificerar att en viss andel av detta anslag skall användas för EMF-forskning.

Introduction

This year's report includes a preamble in which the work process of the IEG is described. In particular the methods for evaluation of the results of studies as well as for synthesizing the scientific evidence within a research area are described. The main part of the report is divided into one section on ELF and another section on RF. Each of these sections discusses both experimental and observational studies. The report also comments upon a review from the UK on the possible relation between EMF and the hormone melatonin. In addition, the report includes a section that discusses newly emerging biological techniques that are of potential importance to laboratory EMF research.

In last year's report the concluding section listed some key issues on which it was considered possible to assess the scientific evidence based on the review in that year's report and in previous years' reports. This list of key issues has been updated in the current report.

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 rele-

vant 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. It is 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 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 leukemia. 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 on leukaemia and the lack of support for plausible biophysical mechanisms of action leads to a rather weak overall evaluation: in IARC's terminology ELF magnetic fields are considered as 'possibly carcinogenic to humans' (Group 2B).

Extremely Low Frequency (ELF)

Recent biology papers

Genotoxicity

A few recent studies have further investigated genotoxicity of ELF magnetic fields. McNamee et al. 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]. Brain cells were investigated for DNA damage at 0, 2 and 4 h after exposure using the alkaline comet assay. Six animals per group were used. Increased DNA damage was observed in response to the positive control (2 Gy X-rays), but no significant increase was found following exposure to any magnetic field intensity at any time after exposure. Thus, the data do not provide support to the earlier findings of, Lai and Singh who reported increased DNA damage in similar experiments with rats exposed for 2 or 4 h at 0.1 - 0.5 mT [Lai and Singh 1997], but note that exposure was short and the number of animals per group small.

Frahm et al. did not find any increase in micronuclei in mouse macrophages exposed for 12, 24 or 48 h at 1 mT [Frahm, et al. 2006], but the experiment (only three independent experiments) had limited statistical power to detect small effects. In the same study, increased production of reactive oxygen species (ROS) was observed after 45-min exposure of macrophages at 0.05, 0.1, 0.5 or 1 mT, with little dependency on magnetic flux density. Significantly increased phagocytosis and interleukin-1β production after exposure at 1 mT also indicated stimulation of macrophage activity.

Fatigoni et al. used plant cuttings (the Tradescantia micronucleus assay) to investigate genotoxicity of ELF magnetic fields. Exposure to 50-Hz magnetic fields at 1 mT for 1, 6 or 24 h resulted in increased frequency of micronuclei [Fatigoni, et al. 2005]. The size of the effect increased with increasing duration of exposure; almost 5-fold compared to the controls after 24 h of exposure. As these experiments were performed using plants, their relevance to human health is unclear. The Tradescantia micronucleus assay has been shown to respond to many genotoxic agents relevant to human health, but there is little information about false positive responses in this assay.

In a study with bacterial cells (Salmonella), no increase of recombination events (used as indicator of DNA strand breaks) was found in cells exposed to intermittent (5 min on, 10 min off) 60 Hz fields at 14.6 mT for 4 h [Williams, et al. 2006]. However, a similar magnetic field exposure provided protection against subsequent heat stress induced by 10 min at 53 °C. Viability of the magnetic field exposed cells was 10 times higher than that of the control cells ($p<0.0001$).

Combined effects with other physical or chemical agents

Effects of combined exposure to ELF magnetic fields and chemical exposures were investigated by [Moretti, et al. 2005]. Jürkat cells were exposed to a 50 Hz field at 1 mT for 1 h, and evaluated for DNA strand breaks using the alkaline comet assay. In the co-genotoxicity experiments, the cell cultures were also simultaneously exposed to the known clastogen benzene or its selected metabolites. Exposure to the magnetic field alone or combined exposure with benzene or 1,2 benzenediol did not increase DNA strand

breaks. However, combined exposure to 1,4-benzenediol and magnetic field led to a clear increase in DNA breaks (about 10-fold, $p<0.01$), although 1,4-benzenediol alone did no induce DNA damage. Moreover, combined exposure to magnetic field and 1,2,4-benzenetriol (which is known for its ability to induce many types of genotoxic effects) led to a significant ($p<0.05$) increase in DNA breaks compared to the effect of this metabolite alone.

Several findings of that type point toward a possible synergy between EMF exposure and other agents. They were reviewed by Juutilainen et al. who gathered data on effects of such co-exposures [Juutilainen, et al. 2006]. It focused on cell culture studies and short-term animal studies that have combined exposure to ELF MFs and known carcinogens or toxic physical or chemical agents, and that are broadly relevant to cancer. The review collected 65 studies published between 1986 and 2002. The results of this quantitative analysis showed a surprisingly high percentage of positive studies, suggesting that MFs do interact with other physical and chemical exposures. All studies on apoptosis and embryotoxicity were positive while it was not the case for genotoxicity. TPA and ionizing radiation were the most efficient agents in inducing the effects. Most of these studies on combined effects used magnetic fields of 100 μT or higher. The dose-reponse relationship showed a minimum at field strengths between 1 and 3 mT. Based on this observation, the authors suggested that the radical pair mechanism (discussed in more detail below) could explain combined effects with agents inducing free radical production and the nonlinear dependency on magnetic field strength found in the analysis. The overall conclusions are not directly relevant for explaining the epidemiological findings of an association with childhood leukaemia above 0.4 μT, as only a few of the studies reviewed had tested fields below 100 μT. However, if adverse effects at 100 μT and above were confirmed, it would have implications for risk assessment and management, since the current critical effect level is at 5000 μT, with a reduction factor of 50 (the "critical" effect is defined by ICNIRP as the health effect seen at the lowest exposure level).

Current overall conclusion on genotoxicity

The majority of previous animal and in vitro studies have found no evidence of genotoxic effects of ELF magnetic fields at field strengths relevant to human exposure. The results of recent studies have not strengthened the evidence of genotoxic effects from ELF magnetic fields alone. However, the combined effects reported by [Moretti, et al. 2005], as well as the interaction with heat stress reported by [Williams, et al. 2006], suggest that ELF magnetic fields might modify biological responses to other chemical and physical agents. While these individual findings have not been confirmed in independent experiments, they are consistent with the results of the recent quantitative review described above [Juutilainen, et al. 2006].

There is also a plausible mechanism (radical pair mechanism [Brocklehurst and McLauchlan 1996], discussed in more detail below) that may explain combined effects with agents inducing free radical production. Most of the studies on combined effects used magnetic fields of 100 μT or higher, which is also close to the current theoretical understanding of the lower limit of the radical pair mechanism. Thus, the findings are not directly relevant for explaining the epidemiological findings suggesting increased risk of childhood leukaemia above 0.4 μT. However, only a few of the studies reviewed had even tested fields below 100 μT.

ELF mechanisms

In the previous SSI expert-group reports, the mechanisms of the effects of ELF magnetic fields were not reviewed, although knowledge about such mechanisms is needed for the interpretation of published health effects at low exposure levels. For a discussion of mechanisms and other data please refer to the preamble.

In 2006, Swanson and Kheifets published a review on mechanisms relevant to environmental exposures to power frequency ELF fields [Swanson and Kheifets 2006], in line with the short summary presented here.

Only the most relevant mechanisms or hypotheses are described below that are either used in setting guidelines or under active testing.

The present exposure limits are based on well-known effects resulting from electric currents induced in tissues by exposure to electric or magnetic fields. The level of the critical effect is set at 5000 μT at power frequency and corresponds to the excitation of nerves and muscles. There are discussions about the use of magneto-phosphenes (visual flicker that are observed in the dark when the eye is exposed to e.g. 20 Hz 7 mT) as the basis for the "critical" effect. Moreover, further debate exists about changing the "metric" (i.e. the physical quantity chosen to define the exposure limit) from current density (A/m^2) to electric field (V/m) to increase its relevance to actual biological effects caused by exposure to magnetic fields.

The effects that form the basis of current exposure limits require high fields (millitesla and higher) and/or field gradients that are not likely to be present in the general environment (where average levels are below 1 μT), although they might sometimes exist in working environments.

However, there are some mechanisms that have been discussed recently as potentially operating at low exposure levels, see for example the review by Engström [Engström 2004]. Some of them are involved in the navigation of non-human species.

Magnetic resonance

Some authors have suggested narrow bandwidth mechanisms involving magnetic resonance phenomena, such as cyclotron resonance, Larmor precession, or ion parametric resonance [Engström 2004]. However, there is no convincing experimental evidence to date of the validity of these mechanisms involving one or two associated fields (e.g. parallel DC and AC magnetic fields).

Biogenic magnetite

It is well known that magnetite crystals, which are tiny magnets, are present in the body of many living species, including the brain. However, the role of these particles is not known with the exception of their role in navigation in some animal species (see below).

Radical pair mechanism

The "radical pair mechanism" is one of the most plausible hypotheses for explaining effects of static and ELF magnetic fields at low levels (below 1 millitesla) [Brocklehurst and McLauchlan 1996; Timmel and Henbest 2004]. Scission of a covalent bond in bio-

logical molecules results in the formation of a radical pair. If the radical pair lives long enough, a magnetic field can affect the probability of its recombination and thereby change the reaction yield. There is ample experimental evidence for this mechanism in biochemical systems but less so for biological systems. Some evidence of that type of biological processes is given by the results obtained on navigation of animals (see below).

Animal navigation

Roles for magnetic fields have been found in several animal species such as birds, fish and newts. Birds are known to use the geomagnetic field as a source of compass information. The vector of the geomagnetic field provides animals with directional information, while intensity and/or inclination provide them with positional information.

There are two processes underlying the avian magnetic compass, one involving magnetically sensitive chemical reactions, the other magnetite crystals. In 2004, Ritz et al. showed that the radical pair mechanism was the basis of one of the bird magnetic senses [Ritz, et al. 2004]. Further work has shown that magnetite crystals also play a role, as demagnetization using a strong magnetic pulse affects this sense. In conclusion, birds use both mechanisms. These pieces of evidence [Thalau, et al. 2005; Wiltschko and Wiltschko 2006], together with electrophysiological and histological studies, suggest that a radical pair mechanism located in the right eye provides directional information (compass), while a magnetite-based mechanism located in the upper beak records magnetic intensity, providing positional information.

It is likely that such processes are present in other animal species, such as newts. However, the fact that magnetite has been found in humans gives no firm evidence for a “lost navigation sense”.

Recent epidemiology

Kabuto et al. conducted a case-control study of leukaemia in children aged 15 years or less and diagnosed between 1999 and 2002 in five geographical regions covering 53.5% (10.7 million) of the total children in Japan [Kabuto, et al. 2006]. For each case, up to 3 controls were selected from the resident registration system matched on gender, age and residential area. Exposure assessment included 1-week measurements made in the child’s bedroom. The distance from each house to the closest overhead power transmission line (22 kV- 500 kV) located within 100 meters was measured. In order to reduce possible information bias due to seasonal variation of MF levels, MF measurements for each set of case and controls were made close in time and within 2.6 days on average. From 1439 childhood leukaemia cases diagnosed in all of Japan, request for participation was sent to the 781 cases living in the selected study areas. The final analysis was based on 251 ALL (acute lymphoblastic leukaemia) and 61 AML (acute myelocytic leukaemia) cases and 495 and 108 controls, respectively. All conditional logistic regression analyses were adjusted for mother’s education as an indicator of SES. When compared with children who were exposed to magnetic fields <0.1 μT, the odds ratios for exposure ≥0.4 μT were 2.63 (95% CI: 0.77-8.96) for all leukaemia combined. No elevation in risk was observed below 0.4 μT. The risk was higher for ALL 4.73 (1.14-19.7) and the risk was not increased (no cases in the highest category) for AML. Initial expectation that this population will have a large number of highly exposed did not materialize. Additionally the low response rate was a limitation of this study.

Unlike the previous studies which have focused on the role of EMF in the development of childhood leukaemia, Foliart et al. examined the association between magnetic field (MF) exposure and survival among children with acute lymphoblastic leukaemia (ALL) [Foliart, et al. 2006]. The children diagnosed and treated in the Paediatric Oncology Group centres between 1996 and 2001 were enrolled in the study (N=482). All children in these centres are enrolled on therapeutic protocols and receive central pathology review and uniform outcome assessment. Only 29% of potentially eligible children participated. Exposure assessment consisted of 24-hour personal MF measurements collected shortly after child's remission. Children were followed up (median follow-up five years) for event-free survival (time from diagnosis until first treatment failure, relapse, secondary malignancy, or death) and overall survival. Adjustment was made for main prognostic factors, such as NCI risk group, race/ethnicity, immunophenotype, and socioeconomic status (SES). Less common prognostic factors such as DNA Index, platelet count at diagnosis, presence of central nervous system involvement at diagnosis, trisomies 4 and 10, trisomy 21, trisomy 8, and several relatively rare cytogenetic translocations including t(9;22), t(4;11), and t(1;19) were also examined. Adjusting for the NCI risk group and socioeconomic status, the event-free survival hazard ratio (HR) for children with measurements ≥0.3 μT was 1.9 (95 per cent CI 0.8, 4.9), based on five failures, compared to <0.1 μT. For survival, elevated HRs were found for children exposed to >0.3 μT (multivariate HR = 4.5, 95 per cent CI 1.5-13.8), based on four deaths among 19 children. This study is the first of its kind and needs to be replicated in further studies.

Savitz and co-authors conducted a study to investigate whether the association between ELF magnetic field exposure and miscarriage could be explained by confounding from physical activity [Savitz, et al. 2006]. The study was triggered by two previous reports that found an elevated risk of miscarriage related to maximum magnetic field levels obtained from personal monitoring of magnetic fields during 24 h [Lee, et al. 2002; Li, et al. 2002]. Savitz et al. hypothesized that women with healthy pregnancies are less physically active, and would therefore have lower magnetic field levels, than women with pregnancy losses because of a higher prevalence of nausea early in a healthy pregnancy, and because of the increased size later in the pregnancy. The authors recruited 100 pregnant women to wear an Actigraph accelerometer and an Emdex magnetic field meter during 7 days. Measurements were summarized into person-minutes, person-days, or person-week. A positive association was found between physical activity and magnetic field levels in the person-day analysis, especially for the highest cutpoints (1.6 or 2.0 μT), but for the person-minutes analysis an association was found only among women who did not work outside home. No associations were found when measurements were aggregated over a week. The influence of nausea on activity was not evaluated. The fact that physical activity and peak measurements were associated when person-day (within as well as between women) served as the analytic unit, but not when the woman was used as the unit, suggests that a given woman was more likely to have a high peak reading on days when she was also more physically active. This observation has little relevance to the question as to whether a woman who has reduced physical activity due to a healthy pregnancy also has less likelihood of a high peak magnetic field exposure. Thus a question whether there is potential for distortion of associations between personal measurements of magnetic field exposures and any health outcomes that might be related to physical activity remains open.

Elwood [Elwood 2006] contrasted the conclusions of three selected studies [Linet, et al. 1997; McBride, et al. 1999; UKCCS 1999] interpreted as no evidence for an association,

to the positive findings of two pooled analyses by Ahlbom et al. [Ahlbom, et al. 2000] and Greenland et al. [Greenland, et al. 2000]. Elwood argued that these discrepancies may result from shortcomings of the pooled analyses, and suggested that the conclusions of the original studies may be more valid. In a commentary, Kheifets et al. [Kheifets, et al. 2006] argue that his analysis involves several conceptual and methodological oversights which undermine his conclusion. Ultimately, of course, the pooled estimate relies on the quality of individual studies; nevertheless, the pooled results remain the most precise and valid estimates for the association between ELF magnetic fields and childhood leukaemia.

Current overall conclusion on epidemiology

The Kabuto childhood leukaemia study is in line with previous epidemiologic findings. The survival study provides a fresh approach and can be important for understanding the potential role of EMF for both development and treatment of childhood leukaemia, but it needs replication. Neither of these results changes the overall IARC conclusions.

Radiofrequency (RF)

Recent laboratory studies

Genotoxicity

Vijayalaxmi et al. expressed concerns about the methods and interpretation of data in two REFLEXstudies that reported increased DNA strand breaks in cells exposed to RF or ELF fields [Vijayalaxmi, et al. 2006]. These studies [Diem, et al. 2005; Ivancsits, et al. 2005] have been reviewed in the previous SSI report [IEGEMF 2005]. In their response to Vijalyalaxmi et al. the REFLEX authors [Rüdiger, et al. 2006], presented the original raw data from their initial study [Diem, et al. 2005]. Examination of the raw data confirmed that the statistical methods used in the original paper were indeed incorrect, as suggested in the previous SSI report [IEGEMF 2005] and by Vijayalaxmi et al. [2006]. However, the raw data also indicate that there are statistically significant differences between the RF field exposed and sham-exposed cultures, detectable with more appropriate statistical methods. In any case, the interpretation of the findings is difficult. As pointed out by Vijayalaxmi et al. [2006], the reported effect might result from increased apoptosis rather than field-induced DNA damage, since apoptotic cells also exhibit DNA fragmentation and could be classified into the highest damage categories in the comet assay as used by the authors. Independent replication and better understanding of the findings is needed before conclusions can be drawn.

Several recent studies have reported no effects of RF fields on various genetic endpoints in cultured cells, such as micronucleus frequency, bacterial reverse mutations, DNA strand breaks, chromosomal aberrations, and sister chromatid exchange [Chang, et al. 2005; Komatsubara, et al. 2005; Sakuma, et al. 2006; Scarfi, et al. 2006; Stronati, et al. 2006]. Frequencies from 835 to 2450 MHz and several different mobile phone signals were used in these experiments. Exposure times varied from 2 to 48 h, and SAR values from 80 mW/kg to 100 W/kg. Stronati et al. [2006] carried out extensive experiments with human lymphocytes to investigate the effects of 24-h exposure to GSM-type 935 MHz fields at 1 or 2 W/kg, alone or in combination with x-rays given before of after the RF field exposure [Stronati, et al. 2006]. The endpoints included DNA strand breaks (alkaline comet assay), chromosomal aberrations and sister chromatid exchange, micronuclei in cytokinesis-block binucleate lymphocytes and nuclear division index. No effects of RF fields alone were observed in any of the endpoints, and RF fields did not modify the effects of x-rays.

Two papers from a Swedish research group report results from exposure of human lymphocytes to GSM-modulated RF fields at 915 or 905 MHz [Belyaev, et al. 2005; Markova, et al. 2005]. The RF field exposures were 1 or 2 h at 37 mW/kg. Lymphocytes from both healthy subjects and persons reporting hypersensitivity to electromagnetic fields were used. Changes in chromatin conformation, which are indicative of stress response and genotoxic effects, were measured by anomalous viscosity time dependence (AVTD), a method described earlier by one of the authors. Tumour suppressor p-53 binding protein 1 (53BP1) and phosphorylated histone H2AX (γ-H2AX), which have been shown to colocalize in foci with DNA double strand breaks, were measured by immunofluorescence. The changes seen after RF exposure (decreased AVTD values, decreased 53BP1 and γ-

H2AX foci) were similar to those induced by heat shock. No significant differences were observed in the responses of lymphocytes from healthy and hypersensitive subjects. The AVTD method is not a standard method generally used by other investigators. A major difficulty with the interpretation of the 53BP1 and γ-H2AX results is that a slight inhibition of an already low background level about (1-2 foci per cell) is reported. The background level can vary depending on many factors, including the stage of the cell cycle. In comparison, genotoxic exposures typically result in clear increase in the number of foci (tens of foci per cell). In any case, the direction of the changes observed was opposite to those induced by genotoxic exposures (but similar to those induced by heat shock), so the results do not provide evidence of genotoxic effects. Possible relevance of the reported changes is unclear, and the positive findings have not been confirmed in independent experiments.

Two recent studies have evaluated genotoxicity after long-term exposure of animals. This kind of experiments can be considered to more closely resemble human situation than the in vitro studies described above. Gorlitz et al evaluated induction of micronuclei in erythrocytes of peripheral blood and bone marrow, in keratinocytes and in spleen lymphocytes of mice exposed RF radiation for 1 or 6 weeks, 2 h per day [Gorlitz, et al. 2005]. Ten female and 10 male animals per group were exposed to two mobile phone signals (GSM at 902 MHz and DCS at 1747 MHz). A complex exposure schedule was used, simulating various elements of exposure during use of a mobile phone. SAR values were highest in the beginning of each 2-h exposure session, and decreased to 0.7 times the initial value after 40 min and to 0.26 times the initial value after another 40 min. The initial (maximum) SAR levels of the three exposure groups (high, medium, low) were 4.0, 1.33 and 0.44 W/kg in the 1-week experiment, and 3.0, 1.0 and 0.33 W/kg in the 6-week experiment. The RF field exposures did not increase the frequency of micronuclei in any of the cells investigated. Although exposure durations were longer than in cell culture studies, this was not a life-time exposure study. As part of the CEMFEC study, Verschaeve et al. investigated possible combined genotoxic effects of RF fields with the drinking water mutagen and multi-site carcinogen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone [Verschaeve, et al. 2006]. Female rats, 72 animals per group, were exposed to GSM-type, 900 MHz RF fields for 2 years, 2 h per day, 5 days per week at whole-body average SAR values of 0.3 or 0.9 W/kg. Blood samples were taken at 3, 6 and 24 months, and brain and liver samples at the end of the study. DNA strand breaks were assessed in all samples with the alkaline comet assay, and micronuclei were determined in erythrocytes. No evidence of enhanced DNA strand breaks or micronuclei was observed in the RF field exposed animals compared to MX exposure only. The limitation of this study is that it did not test very high exposure levels which are the normal approach in toxicological testing of chemicals.

Current overall conclusion on RF genotoxicity

Evidence on genotoxicity of RF electromagnetic fields has been reviewed recently [Verschaeve 2005; Vijayalaxmi and Obe 2004], and some recent studies were reviewed in the previous SSI report [IEGEMF 2005]. The effects of RF fields on many different genotoxicity endpoints have been evaluated both in vitro and in vivo using a wide range of exposure levels, and most of the studies have reported no effects. The most recent studies reviewed for the present report do not appear to strengthen the evidence of any genotoxic effects of RF fields. The results of the REFLEX project reporting increased

DNA strand breaks in cell cultures exposed to RF fields are difficult to interpret and need independent confirmation before conclusions can be drawn.

Human laboratory studies

Several studies published in 2006 which have examined the effects of mobile phone RF radiation on cognitive performance and on the electrical activity of the brain are discussed below. In addition, a number of studies published in 2006 have examined cognitive performance effects in individuals who report subjective symptoms such as warmth sensations on and around the ear, burning sensations in the skin, and a greater prevalence of headaches in response to mobile phone use. People reporting such symptoms in relation to RF and/or ELF exposure are usually deemed to show "electromagnetic" or "electrical hypersensitivity" (see SSI report 2004 for discussion [IEGEMF 2004]). These studies have also examined well-being and a number of physiological parameters such as heart rate variability. One study in particular [Regel, et al. 2006] is a follow-up to the widely discussed 'TNO study' [Zwamborn, et al. 2003] of the effects of exposure to RF radiation emitted by mobile phone base stations on cognitive performance and subjective reports of well-being in people considering themselves to be "hypersensitive" to RF fields compared to effects seen in non-sensitive individuals.

Cognitive function

Russo et al. investigated the effects on cognitive performance of exposure to 888 MHz CW or GSM RF radiation using a relatively large number (168) of male and female volunteers compared to the earlier studies, increasing the statistical power of the study [Russo, et al. 2006]. The subjects were exposed or sham-exposed in two sessions, separated by a week. Half of the subjects had the left side of the head exposed, and half the right side, irrespective of their handedness. Unlike most previous studies, the RF exposure was carried out under double-blind procedures. Cognitive performance was assessed using similar tasks to those used previously, viz: reaction time task, 10-choice serial reaction time task, subtraction task and vigilance task, which were administered in a counterbalanced order. The authors found no significant effects of RF exposure on task performance, irrespective of whether the left or right side of the head was exposed.

Keetley et al. investigated the effect of exposure to GSM RF radiation on the cognitive performance of 120 male and female volunteers using a double-blind crossover design [Keetley, et al. 2006]. The subjects were exposed or sham-exposed in two sessions, separated by a week. Cognitive performance was assessed using a battery of eight cognitive tests: Rey's audio-visual learning test, digital span test, digital symbol substitution test, speed of comprehension test, trail making task, reaction time task, choice reaction time task and inspection time task, which were administered in a counterbalanced order. After adjusting for known covariates (gender, age and education), simple and choice reaction times showed significant impairment, in contrast to earlier studies [Koivisto, et al. 2000; Preece, et al. 1999], whereas performance on the trail making task, which involves working memory, significantly improved. The authors point out that neither of the earlier studies corrected for known covariates, and that the study of Koivisto et al [2000b] used only a single-blind study design.

Eliyahu et al. examined, in 36 young, right-handed male subjects, the effects of GSM mobile phone RF radiation exposure of the right or left side of the head on four cognitive

tasks selected for high cerebral hemisphere specificity [Eliyahu, et al. 2006]. The authors' intention was to examine the effect of RF exposure of a specific part of the brain on associated cognitive functions. The tasks were a spatial item recognition task (activating the right premotor cortex), a verbal item recognition task (activating the left posterior parietal cortex and supplementary motor and premotor cortex), and two spatial compatibility tasks (a visual stimulus on the left side of the test screen activating the left posterior parietal cortex, and on the right side activating the right posterior parietal cortex). Each task required right- and left-handed responses. The subjects were exposed or sham exposed in two sessions, separated by 5 minutes. The study was conducted under single-blinded conditions, and the exposure regime and task sequence were counterbalanced. The authors analysed the reaction times for correct responses to each task, comparing the exposure condition (left, right or sham) for left hand or for right hand responses. Generally, right-hand responses were faster than left-hand responses (the subjects were right-handed) and strong training effects (reaction times faster in the second session) were present in most sham responses. The authors reported that RF exposure of the left hemisphere of the brain resulted in slower left-hand responses in the second session compared to the first for two tasks: the spatial item recognition task, thought to activate the right premotor cortex, and one spatial compatibility task, where left-handed responses are thought to activate the left parietal cortex. Thus, no correlation was seen between exposure of the left hemisphere and the hemisphere-dependence of the two affected tasks.

Event-related (or evoked) electrical potentials in the brain

The electrical activity of the brain, assessed from electroencephalogram (EEG) recording, is complex and difficult to interpret but can be used to provide useful diagnostic information regarding the functional state of the brain, not only from recordings of the spontaneous activity at rest but also from recording the electrical activity resulting from the sensory responses and subsequent cognitive processes evoked by specific sensory stimuli (event-related or evoked potentials). A major difficulty with interpretation of the EEG in individuals at rest is that the intra-individual variability is very high. The variability of event-related potentials (ERPs) is much lower, resulting in better reproducibility, and has often been used to investigate the effect of mobile phone RF radiation. Nevertheless, interpretation is still problematic, since changes in arousal and attention of volunteers can substantially affect the outcome of these studies.

Krause et al. examined the effects of mobile phone RF radiation on event-related oscillatory EEG responses in children [Krause, et al. 2006]; different frequencies of brain electrical activity that have been associated with distinct aspects of cognitive functioning such as stimulus processing, attention and working memory. For example, EEG oscillations in the 4-8 Hz band have been related to the encoding and the retrieval of information. The authors examined event-related desynchronisation (ERD), which reflects a relative decrease in the power of a specific frequency band during stimulus processing (compared to a no-stimulus reference), and event-related synchronisation (ERS), which reflects a relative increase in power, in 15 children aged between 10-14 years performing an auditory memory task. A standard 902 MHz GSM mobile phone was mounted at a set location over the head left posterior temporal region of each subject; each EEG recording was subdivided two 30 min segments, one with the phone switched on, the other with the phone switched off. The study design was double-blind and the exposure order counterbalanced across participants. RF exposure resulted in statistically significant differences in ERD/ERS responses in the 4-8 Hz frequency band during encoding and recognition tasks

at several recording sites on the skull, and at ~15 Hz at one site during the recognition task. However, EEGs are difficult to interpret; Krause et al. indicate that the results are congruent with those of earlier studies [Krause, et al. 2004; Krause, et al. 2000]; see [IEGEMF 2004].

Hamblin et al. investigated the effects of RF exposure on reaction time and the amplitude and latency of auditory and visual ERPs using a large number of subjects (120) in a double-blind, counterbalanced, crossover design [Hamblin, et al. 2006]. Two experimental sessions were held, one week apart; in each session subjects were initially sham exposed, and then either exposed or sham exposed to 895 MHz (GSM) RF radiation. The authors measured the reaction times for cognitive responses to an auditory and a visual cognitive (oddball) task and recorded the early and late components of ERPs resulting from the auditory and visual stimuli. In contrast to the results of an earlier study [Hamblin, et al. 2004], there were no statistically significant effects on the early or late components of the ERPs, and no effect on reaction times. The authors concluded that there is currently no clear evidence in support of a mobile phone related EMF effect on ERPs or reaction times.

Yuasa et al. studied the effects of mobile phone RF radiation on somatosensory ERPs in 12 subjects [Yuasa, et al. 2006]. The experiment was single-blinded. Exposure or sham exposure was to 900 MHz RF radiation from a digital mobile phone held by hand for 30 min within 4 cm of the head. The authors recorded the ERP in the sensory region of the right cortex evoked by median nerve stimulation of the left arm before during and after exposure. The authors reported that the RF exposure did not affect the somatosensory ERP, nor its recovery function, suggesting that neither the neural pathways mediating somatosensory stimuli nor the large neurons of the sensory cortex are affected by mobile phone radiation.

Maby et al. investigated the effects of GSM RF radiation on auditory ERPs recorded before and during exposure or sham exposure [Maby, et al. 2006]. The experimental design was single-blinded. Following the reported elimination of artefacts resulting from electrical pick-up, the authors characterised various electrophysiological parameters, such as the amplitude and latency of the N100 and P200 waves of the ERP signal, and compared the effects of the GSM signal on these parameters in nine normal and six epileptic subjects. The authors reported that a decrease in the N100 latency and amplitude was seen in normal subjects on the side of the head adjacent to the mobile phone, whereas in epileptic patients, an increase in N100 latency was seen on the contralateral side of the head. However, it is not clear if or how the authors corrected for multiple comparisons.

Ferreri et al. investigated the effects of GSM mobile phone RF radiation on cortical excitability in fifteen right-handed young male volunteers using transcranial magnetic stimulation applied to the motor cortex before and after RF exposure in order to generate motor-evoked potentials in a target muscle in the hand [Ferreri, et al. 2006]. The volunteers, who were right-handed, and were instructed to avoid caffeine, alcohol and medication before each trial, were screened for predisposition to epileptic seizures. All subjects underwent two trials, separated by one week, in a double-blind cross-over experimental design. The left side of the subject's head was exposed or sham exposed to RF radiation for 45 min; the right side served as a control and a 'paired-pulse TMS paradigm' was applied to each hemisphere before, immediately after, and 1 hour after exposure. The main effect, which was of borderline statistical significance ($p=0.07$), was a transient decrease in intracortical inhibition and a transient increase in intracortical facilitation in the RF-exposed hemi-

sphere. However, the analysis and interpretation is complex; further replication, perhaps using larger numbers of subjects, would be appropriate.

Cognitive studies, well-being and physiological effects in "RF-sensitive" people

As mentioned above, a follow-up of the study by Zwamborn and co-workers [Zwamborn, et al. 2003] has been recently published by [Regel, et al. 2006]. These authors note that other follow-up studies to the 'TNO study' have been initiated in Denmark, the UK and Japan. Briefly, the earlier study, which was double-blind, found that both "RF-sensitive" and non-sensitive subjects reported significantly lower well-being following exposure to third-generation 2140 MHz (UMTS) RF radiation but not to second-generation 945 MHz (GSM) or to 1840 MHz (GSM) RF radiation. In the four cognitive function tests, statistically significant differences were seen more often than should occur by chance, but there was no consistent pattern of response across the three signals, the different cognitive tasks or the two study groups [AGNIR 2003; IEGEMF 2004]. Some of the comparisons between exposure and sham conditions that were reported as significant might be due to chance [AGNIR 2003].

The follow-up study by Regel et al. [2006] investigated the effect only of the 2140 MHz UMTS base-station-like RF signal, identical to that used by Zwamborn et al., on well-being and cognitive performance in thirty three RF-sensitive subjects and in eighty four non-sensitive subjects. There were three experimental sessions held at one week intervals; subjects were randomly assigned to one of six possible sequences of three exposure conditions, each lasting 45 min: 0 V/m (sham), 1 V/m (identical to that used by Zwamborn et al.), and 10 V/m (in order to assess any possible dose-response relationship). Peak spatial SARs in the brain (averaged over 10 g) were around 45 μW/kg at 1.0 V/m, and about 4.5 mW/kg at 10 V/m, well below ICNIRP guideline values. The study was double-blinded with a randomised cross-over design. Well-being was assessed using three standard questionnaires, one of which was identical to that used in the earlier study. Cognitive performance was assessed using a simple reaction time task, a 2-choice reaction time task, the N-back task and the visual selective attention task, the latter also used by Zamborn et al. [2003]. In order to control for false positive findings resulting from multiple testing, Regel et al. [2006] carried out multiple endpoint adjustment. In addition, the results were adjusted for possible confounding by a number of possible factors including age, gender, caffeine intake, medication, etc.

The results of the present study differ with respect to both well-being and cognitive performance from the results reported by Zwamborn et al. [2003]. Well-being was not affected by UMTS radiation at either exposure level. Even though RF-sensitive subjects generally reported more health problems, Regel et al. [2006] found no difference between the two groups with respect to the applied field conditions. Similarly, cognitive performance was not affected, except for two separate and marginal effects at the higher level of exposure: speed was affected in the RF-sensitive group in one (choice reaction time task) of six cognitive tasks, and accuracy in the non-sensitive group in one (1-back task) of five tasks. However, these effects did not reach significance after adjustment for multiple endpoints. Contrary to the TNO study, Regel et al. [2006] found no significant effect on speed in the visual selective attention task, which was the only task used in both studies. Overall therefore, no clear picture emerged across the two studies showing reproducible effects of exposure condition or cognitive task.

Regel et al. [2006] point to the other various improvements in their study compared to the earlier study, regarding specifically 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 effects (controlling for time of day) and carry-over effects between sessions (since the interval between experimental sessions was substantially increased). However, the authors conclude that although no causal relationship between RF EMF and a decrease in well-being or adverse health effect was found under the given exposure conditions, an effect of UMTS-like EMF on brain functioning could not be excluded.

Another recent study [Wilen, et al. 2006] investigated the effects of mobile phone radiation on various physiological parameters such as heart-rate variability, electrodermal activity, and respiration rate in twenty subjects who considered themselves to be "hypersensitive" to mobile phone RF radiation and in twenty non-sensitive subjects, matched with respect to age, gender and occupation. These parameters were measured before, during and after exposure. In addition, tests of arousal and vigilance, short-term memory and reaction times were performed before and after exposure. All subjects were exposed or sham exposed to 900 MHz (GSM) RF radiation for 30 min on two separate days, one day with sham exposure and one with true exposure, presented in a random order, so that each subject served as their own control; the study was single-blinded. Physiological data were analysed using multivariate analysis of variance and cognitive task performance analysed using repeated-measures analysis of variance, both corrected for multiple comparisons. No significant effects of RF radiation on any physiological or cognitive variable were found in either group. However, regardless of exposure status, people who considered themselves to be "hypersensitive" to mobile phone RF radiation showed differences in heart-rate variability and in tests of critical flicker-fusion threshold and memory compared to non-sensitive subjects, perhaps reflecting differences between these two groups in autonomic nervous system function.

Rubin et al. investigated the effect of exposure to GSM mobile phone radiation on the severity of the symptoms experienced by 60 subjects who identified themselves as sensitive to such radiation, compared to 60 'non-sensitive' subjects [Rubin, et al. 2006]. Each subject was exposed or sham exposed for 50 minutes either to a pulsed 900 MHz GSM signal or to a non-pulsed signal, both of which induced a localised SAR in the region of the head adjacent to the phone of 1.4 W/kg. There were three separate experimental sessions over a two year period within which the order of presentation was randomised and counter-balanced. All subjects were asked to score on visual analogue scales before, during and after exposure, the severity of headaches and various other symptoms such as nausea, fatigue, dizziness. The authors found that the proportion of sensitive participants who believed a signal was present during GSM exposure (60%) was similar to the proportion (63%) who believed one present during sham exposure. In addition, the prevalence of various symptoms experienced during exposure or sham exposure in people who reported themselves as GSM-sensitive was very much higher than in non-sensitive subjects, but this occurred irrespective of the exposure condition. In some cases, for sensitive subjects, the symptoms experienced were so severe that the individual withdrew from the study. Rubin et al [2006] suggested that psychological factors, possibly the conscious expectation of such symptoms, might have a key role in the aetiology of this condition.

Conclusions

The recent volunteer studies have not clarified conclusions regarding possible mobile phone RF effects on cognitive function; the results are inconsistent, but no single clear effect on cognitive function can be identified. In general, however, the many well-conducted studies published recently report failures to replicate smaller, less methodically rigorous studies reporting positive findings a few years ago.

Evoked or event-related potentials (ERPs) are more reproducible and less variable than EEG recordings. Most recent well-conducted studies indicate a lack of effect of mobile phone RF radiation on ERPs.

A replication of the TNO study in which the experimental protocol was significantly improved did not find effects of UMTS-like base-station RF radiation on cognitive performance and well-being in "RF-sensitive" individuals or in non-sensitive controls, after having adjusted for multiple comparisons.

Otherwise, differences between "RF-sensitive" people and non-sensitive people can be seen in a number of physiological parameters that are strongly influenced by the autonomic nervous system, such as electrodermal activity and heart rate variability, but these endpoints are not influenced by mobile phone RF radiation in either group of volunteers. In addition, people self-reporting as RF sensitive can experience headaches, nausea dizziness and other symptoms during mobile phone use at a very much greater prevalence than non-sensitive individuals. However, this is independent of their exposure status, whether the RF exposure is real or sham, and might reflect a conscious expectation of such effects.

RF mechanisms

Thermal vs. non-thermal

There is a "heated" debate about the existence of "non-thermal" effects of RF at the low levels found in the environment and in mobile telephony in particular, a thermal effect being one due to temperature elevation of the tissue, organ, or organism.

The vast majority of the research projects worldwide deal with the search for non-thermal effects and thresholds.

Several workshops have been devoted to the state of knowledge about mechanisms of RF effects, whether thermal or non-thermal, including two in the fall of 2006 (Rostock in Germany and Erice in Italy).

A review by Challis concluded that there is no valid hypothesis that can explain non-thermal low-level RF effects [Challis 2005].

Basic physics teaches that all RF absorption leads to heating. However at low level (i.e. below exposure guidelines), heating is negligible and "delocalized", that is not affecting specifically cellular or subcellular structures. This is due to the fact that these structures are very small and diffusion is fast.

Transfer of energy into the vibration modes of macromolecules has been suggested but is not possible because of damping of the energy by transfer to other modes and to water molecules [Adair 2003]. Moreover, vibrational absorption starts at ca. 150 GHz far above the frequency range currently used in wireless communications.

Thermoreceptors

The Adair group in the USA [Adair, et al. 2005; Adair 2003] has exposed subjects at various frequencies from 100 to 2450 MHz and at moderate level (90-150 W/m^2) and found out that under certain conditions they thermo-regulate efficiently because of increased heat loss responses, particularly sweating. The authors conclude that these responses are controlled by neural signals from thermo-sensors deep in the brainstem and spinal cord, rather than those in the skin.

The likely candidates are neurons, which initiate appropriate heat loss responses via the hypothalamus.

An approach to non-thermal effects has been recently to ask the question: "are non-thermal effects "subtle thermal" effects, or do they really occur also at weak RF field exposure, according to the biophysical definition, i.e. without temperature elevation." Glaser has put forward the hypothesis that non-thermal RF effects ultimately are the result of thermo-receptor activation [Glaser 2005]. These thermo-receptors (e.g. nerve endings, ion channels) are located on the surface as well as in many other parts of the body of warm-blooded animals, including the brain and the spinal cord. The internal thermo-receptors are mainly responsible for controlling blood temperature. They transmit the information to the centre for temperature control, which is the preoptic area of the anterior hypothalamus. This hypothesis is in agreement with the observations of the Adair group described above.

Demodulation

Since there is evidence of some bioeffects in the ELF range, several investigators have suggested that "demodulation" of the modulated-RF signals occur. However, the only or most likely biological structure known to be non-linear and therefore able to demodulate, is the cell membrane. But, non-linearity has been observed only below approximately 1 MHz, as the membrane becomes transparent to the incoming wave above that frequency. The question is thus whether there are other biological components that are non-linear at ca. 1 GHz. In order to answer that question experimentally, scientists in the USA and UK are performing an experiment looking for the generation of signals at twice the frequency of the wave impinging onto a biological sample [Balzano, et al. 2006]. Awaiting the outcome of this experiment, the consensus is still that if modulation is biologically significant in the frequency range used for mobile telephony, the entire rationale for RF exposure guidelines would need revision, but present evidence does not indicate that this is the case.

Recent epidemiological studies

Mobile phone studies

The German Interphone study [Schuz, et al. 2006a] consisted of all new cases of glioma and meningioma at ages 30-69 years referred to four major neurosurgical departments in Germany between 2000 and 2003, in total 366 glioma and 381 meningioma cases. Cases without histologic confirmation were excluded. Controls were selected from regional population registers with frequency matching by age, sex and region, in total 1494 controls. Exposure assessment was based on interviews similar to other Interphone compo-

nents. Participation was 80% among glioma, 88% among meningioma cases, and 63% for controls. Among glioma cases 11% of interviews were based on proxy respondents. Among the cases, 38% used a mobile phone regularly. The corresponding number for controls was 39%. No association with glioma risk was found for regular use of mobile phones (OR=0.98, 95% CI 0.74-1.29) or cumulative hours of use (OR=1.01, 95% CI 0.64-1.60 for more than 195 hours). Non-significantly increased odds ratios were found for more than 10 years since start of use (OR=2.2, 95% CI 0.94-5.11), intensity of use (OR=1.54, 95% CI 0.75-3.15 for more than 30 minutes per day), cumulative number of calls (OR=1.34, 95% CI 0.86-2.07 for more than 4350 calls) and duration of calls more than five years earlier (OR=1.31, 95% CI 0.7-2.26). For meningioma, no increased risks related to mobile phone use were found. Results on ipsilateral use were not reported, except for a subgroup of cases. Anatomic distribution of the gliomas or meningiomas did not differ among users and non-users. Use of cordless phones was not associated with either brain tumour type. The findings were largely negative, with some indication of increased risk for long-term use, although based on very small numbers (only 12 exposed cases). A separate report addressed exposure to a digital cordless phone (DECT) base station in the bedroom (DECT), but did not show any increased risks [Schuz, et al. 2006b]. This study had a high participation, but statistical power was not quite sufficient for finer stratification or sub-group analyses.

Combined analysis of the two UK centres of the Interphone study included 966 glioma cases and 1716 controls [Hepworth, et al. 2006]. Case ascertainment was through hospitals and regional cancer registries, with controls identified from general practitioners' lists. Of the cases, 97% were histologically confirmed. Of the cases, 51% were successfully enrolled and 45% of the controls were recruited. Proxy interviews were used for 7% of the cases. Among the cases, 53% used a mobile phone regularly, whereas the corresponding number for controls was 52%. Regular use of mobile phones was not associated with glioma risk (OR=0.94, 95% CI 0.78-1.13). No association was found for cumulative years of use, number of calls or hours of use. Separate analyses of low and high grade tumours, as well as analogue phones gave similar results. Use of mobile phone on the side where the glioma was diagnosed (ipsilateral use) was associated with a slight, significant increase in risk (OR=1.24, 95% CI 1.02-1.52). However, a corresponding deficit was found on the opposite side (contralateral use, OR=0.74, 0.61-0.93). The researchers interpreted this as recall bias. This study appears to be of good quality, with low participation as the main weakness, and included a large number of long-term users (48 cases has used a mobile phone more than 10 years).

The Japanese Interphone study has reported the results on acoustic neuroma [Takebayashi, et al. 2006]. The cases were 97 patients with vestibular schwannoma aged 20-59 years and diagnosed in 2000-2004. A total of 330 individually matched controls were selected using random digit dialling. Exposure information was obtained by personal interviews, with participation 84% among cases and 52% among controls. Of the cases, 58% had used mobile phone regularly, and the corresponding figure was 53% for controls. Regular mobile phone use was not associated with increased risk of acoustic neuroma (OR 0.7, 0.4-1.2). Mobile phone use for at least five years had no obvious effect either (OR 1.1; 0.6-2.1). Duration of mobile phone use or cumulative call time were not associated with increased risks. The odds ratio for ipsilateral use was 0.9. The study was relatively small and participation among controls rather low. The number of long-term users was also relatively small.

The results of the Swedish and Danish Interphone studies on parotid gland tumours have been published recently [Lonn, et al. 2006]. The material consisted of 60 malignant and 112 benign cases diagnosed in 2000-2002 at ages 20-69 years, with 681 controls. Cases were ascertained from both hospitals and cancer registries. Controls were identified from population registries. Exposure assessment was based on interviews, similar to other Interphone analyses. Response proportions were 85% for malignant tumours, 88% for benign pleomorphic adenomas and 70% for controls. No increased risks of either tumour type were related to regular mobile phone use, duration of use, time since first use, cumulative call time or cumulative number of calls. Odds ratios for benign tumours were non-significantly above unity for ipsilateral mobile phone use (use on the same side where the tumour was diagnosed), while correspondingly reduced risks were found for contralateral side. The findings were largely negative and the results related to ipsilateral use were interpreted as information bias.

Two combined analysis of two earlier sets of data on mobile phone use and brain tumours and acoustic neuroma was published by Hardell and co-workers [Hardell, et al. 2006a; Hardell, et al. 2006b]. These reports do not essentially add to the earlier publications.

A Danish cohort study has recently been presented [Schuz, et al. 2006c], which is based on a cohort of mobile phone subscribers described earlier [Johansen, et al. 2001]. This new report has extended the follow up through 2002. As a consequence the study now has a considerably larger number cancer cases and a larger number of long-term users. The emphasis in this article is on a comparison of subscribers to non-subscribers, as defined at the beginning of the follow-up. Use of mobile phones was not associated with increased risk for brain tumours (SIR=0.97), acoustic neuroma (SIR=0.73), salivary gland tumours (SIR=0.77), eye tumours (SIR=0.96), or leukaemia (SIR=1.00). Unfortunately the only results for subscribers with more than 10 years duration of use that are presented are for the broad groups brain and nervous system tumours (SIR=0.66 95% CI 0.44-0.95) and leukaemia (SIR=1.08, 0.74-1.52). For none of those tumour groups does the study find increased risks. Indeed, for brain and nervous system tumours the risk is reduced. No data are presented for long term users in relation to more finely specified tumour types which is where more information is really needed. The study does not rely on information from phone users for assessing exposure which is used in most other studies, but uses subscriber information instead. This is an informative alternative but not without its problems, one of which is that the subscriber is not always the actual user of the phone. Also a problem is that corporate users, likely to be among the heaviest users of mobile phones are not in the cohort, but are included in the national incidence rates. In balance, the results of this study do not materially change the current evaluation of potential cancer risks with use of mobile phones.

To evaluate the potential effect of mobile phone use on intracranial tumour risk Lahkola et al. conducted a meta-analysis of all the twelve published studies (which included the total of 2780 cases) [Lahkola, et al. 2006]. From each study risk estimates were obtained for subjects who had used mobile phones for longest periods of time (>5 years in most reports). Fixed or random effects were calculated for all intracranial tumours combined and for different histological tumour types separately (glioma, meningioma, and acoustic neuroma). Additionally, differences in the tumour location and type of mobile telephone network used (NMT or GSM) were evaluated. All summary estimates were close to one, indicating no risk increase. Risk was not increased for various tumour types or locations, or for the analysis of analogue vs digital phone use. This meta-analysis did not find an increased risk of intracranial tumours from mobile phone use for a period of at least five

years. Unfortunately, results were significantly heterogeneous between studies. Furthermore, several limitations of the individual studies influence the interpretation of this meta-analysis. First, exposure assessment remains problematic for the studies conducted: substantial random error has been shown for even short-term recall of mobile phone use; and information bias appears to affect at least the reporting of the side of head where the phone is commonly used. Second, a non-representative control group, due to an increased participation of mobile phone users, appears to be present in some studies. Third, mobile phone exposure is still relatively recent for tumours with long latency, such as brain tumours (which may take up to 20 years to develop). Lastly, even the meta-analysis of twelve studies includes only a small number of subjects with long-term use.

A simulation study explored the potential effect of recall bias and random error in reported mobile phone use on results of case-control studies [Vrijheid, et al. 2006]. The approach was based on Monte-Carlo simulation. First, a base population of 175,000 subjects was generated and assigned a "true" log-normal exposure distribution. Then, disease status was assigned to obtain 1000 cases and 2000 controls. This was repeated 5000 times for each analysis. For assessment of recall bias, a multiplicative error model was used, with reported exposure relative to the actual exposure. Non-differential recall error was found to bias the results toward unity as expected. In case of non-differential random error, bias towards unity occurred when cases had larger uncertainty than controls. Similar dilution resulted also when cases had either over- or underreporting of exposure (but no such phenomenon occurred among controls). Expectedly, underselection of unexposed controls biased the results toward the null, while underselection exposed controls had the opposite effect. Yet, selection bias affected the categorical exposure variables more strongly than continuous ones. The conclusion of the paper was that random error exerts the strongest distortion, when assuming similar magnitude of errors as observed in the validation studies of the Interphone project. Most errors tend to result in underestimation of effects. Though based on simplistic scenarios (addressing one type of error at a time) and assumptions about error structures, the results may be useful in interpreting the findings of the Interphone study.

Symptoms near base stations

A study conducted in Austria evaluated the possible effect of base stations on subjective symptoms and cognitive performance [Hutter, et al. 2006]. The eligible subjects were living in the vicinity of 10 mobile phone base stations. The study population consisted of 336 subjects from both urban (Vienna) and rural (Carinthia) areas. In Vienna, subjects were randomly selected from telephone catalogues, and in Carinthia, houses were randomly selected from a site map. Participation was below 60% in urban and 68% in rural areas; the presentation of the study may lead to recruitment of subjects with health problems and hence introduce selection bias. A spot measurement of electromagnetic field density with spectrum analyser was conducted in the bedrooms of the participants. In addition, the maximum exposure from the base station was computed based on measurements of the broadcast channels. The estimate of the maximum exposure was used in the analyses. Comparisons were made between three exposure groups with average exposure levels of 0.04, 0.23 and 1.3 mW/m^2. Cognitive performance was assessed by memory tasks, choice reaction tasks and perceptual speed tests. No clear difference was found in sleep quality or cognitive performance, but a slightly faster reaction in perceptual speed was associated with higher exposure. Statistically significantly increased 1.3 to 1.6-fold prevalence of three out of 14 subjective symptoms (headaches, cold hands or feet and

concentration difficulties) was reported in the group with the highest exposure after adjustment for age sex, region, mobile phone use and fear of adverse effects of base stations. Adjustment did not cover all determinants of perceived health, for instance sociodemographic factors. Therefore, confounding is an issue. Concern for effects of base stations was also associated with sleep quality. Nevertheless, the study should be replicated elsewhere to further assess the possible health effects. Experimental studies might also contribute to the issue with major advantages of randomisation and controlled environment (though experimental studies are capable of assessing short-term effects only).

Current overall conclusion on mobile phone use

Recently published studies on mobile phone use and cancer risk do not change the earlier overall assessment of the available evidence from epidemiological studies. In particular an extended follow up of a cohort study from Denmark does not alter the conclusions. Currently available evidence suggests that for adult brain tumours there is no association with mobile phone use for at least up to, say, ten years of use. For longer latency the majority of the evidence also speaks against an association, but the data are still sparse. The same conclusion holds for short-term use and acoustic neuroma. However, for long-term use and acoustic neuroma there is a concern, and more information is required. A study on symptoms near base stations did see an association between exposure level and prevalence of symptoms. These results need to be replicated and better understood before conclusions can be drawn.

Newly published reviews

Melatonin

Melatonin is a hormone produced by the pineal gland in a distinct daily or circadian rhythm which is governed by day length; serum melatonin levels are very low during the day and are elevated at night in both nocturnal and diurnal animals, including humans. It has been shown to influence the control of daily activities such as the sleep/wake cycle, and is known to regulate seasonal changes in animal species such as those showing annual reproductive cycles. However, the interactions of melatonin with cells and tissues and the effects on body metabolism and physiology are very complex and not fully understood at present. There are, for example, strong links between circadian clock control, sensitivity to genotoxic stress, growth control and the genesis and development of cancer [Antoch, et al. 2005; Lee 2006; Reddy, et al. 2005].

Stevens suggested that chronic exposure to power frequency electric or magnetic fields might reduce melatonin secretion by the pineal gland and increase the risk of breast cancer [Stevens 1987]. This followed a hypothesis proposing that diminished function of the pineal gland may promote the development of human breast cancer. Other more recent suggestions include the possibility that melatonin can suppress the growth of mammary tumour and other cancer cells, act as a free radical scavenger, at least at pharmacological levels, and affect immune responsiveness. Thus, an effect of EMF exposure on circulating melatonin levels might potentially have wide-ranging implications for health. Two recent reviews have been published and are briefly summarised below.

Power Frequency EMFs, Melatonin and the Risk of Breast Cancer

The UK independent Advisory Group on Non-ionising Radiation (AGNIR) has recently reviewed the relationship between power frequency magnetic fields, melatonin and the risk of breast cancer in humans [AGNIR 2006]. A detailed review of melatonin physiology was presented, along with a critical review of the experimental and epidemiological evidence relating to circulating melatonin levels (or surrogate measures of this) and breast cancer risk. AGNIR also reviewed the effects of EMF exposure on both of these endpoints.

The Advisory Group noted that there is some evidence that altered melatonin levels per se affect breast cancer risk; this was discussed at length in the review but the evidence was regarded as incomplete. Epidemiological studies of melatonin levels in women who later develop breast cancer were regarded as inconclusive [Schernhammer and Hankinson 2005; Travis, et al. 2004], but studies of breast cancer incidence in shift workers, airline cabin staff, and others with markedly altered light/dark cycles, offered indirect support for an effect, as did experimental studies using cell cultures and animals.

With regard to the effects of power frequency magnetic fields on circulating melatonin levels, AGNIR concluded that, overall, the epidemiological studies do not give convincing evidence that residential or occupational exposure have any effect. Although most of the published studies, including the series by Burch et al [Burch, et al. 2002; Burch, et al. 2000; Burch, et al. 1998; Burch, et al. 1999a] of male electrical utility workers, have found some significant results, usually in a subset of the data, there was no consistency in the sub-group for which significant results were found, and indeed in general the significant results were not re-examined for the same sub-group in subsequent studies. Other difficulties in interpretation of many of the studies included differences in the measures of EMF exposure and in circulating melatonin levels used in the different studies, and the likely inadequacy of some surrogate measures, such as the overnight secretion of the major urinary metabolite of melatonin. In addition, the Advisory Group drew attention to the large number of potentially confounding variables that can affect circulating melatonin levels and that need to be taken into account in study design and data analysis including light exposure at night, changes in sleep/wake cycles, posture, caffeine, alcohol and a variety of medications.

The results from experimental studies are also considered equivocal: the majority of volunteer and animal studies report a lack of effect on the rise of circulating melatonin levels at night, but there are some positive studies. For example, two studies with volunteers raise the possibility of effects in responsive sub-groups [Wood, et al. 1998] and over long-term exposure [Graham, et al. 2000]. However, overall, the Advisory Group concluded that laboratory-based studies in humans did not provide consistent support for a field-dependent effect. The strongest evidence for a field-dependent effect in rodents comes from a series of studies with rats exposed to circularly polarised magnetic fields [Kato, et al. 1993; Kato, et al. 1994a; Kato, et al. 1994b; Kato, et al. 1994c] but these results were sometimes weakened by inappropriate comparisons between exposed animals and historical controls. With regard to effects of power frequency EMFs on melatonin levels in seasonally-breeding animals, the evidence is mostly negative, and there were too few data to make any firm conclusions regarding non-human primates, although a preliminary study with baboons reported melatonin suppression in response to an irregular and intermittent exposure [Rogers, et al. 1995]. Studies of the effect of power frequency magnetic fields on melatonin production in isolated rodent pineal cells, although mostly positive, were considered unconvincing for a variety of technical reasons.

Finally, with regard to studies of the effect of EMF exposure on the risk of breast cancer regardless of mechanism, AGNIR conclude that there is no consistent evidence of an effect of EMF exposure. Although there are some positive epidemiological studies, the Advisory Group considered that the scientific literature overall does not support an association between power frequency magnetic field exposure and breast cancer risk. A similar conclusion has previously been expressed by Ahlbom et al, [Ahlbom, et al. 2001]. The data from animal studies are thought equivocal. A series of studies from one laboratory [Mevissen, et al. 1998; Mevissen, et al. 1996a; Mevissen, et al. 1996b; Mevissen, et al. 1993a; Mevissen, et al. 1993b] has reported that power frequency EMF exposure increases chemically-induced breast cancer incidence in rats. However, there was considerable variation in the sham data, and a failure to reproduce similar results in another laboratory [Anderson, et al. 1999; Boorman, et al. 1999] led to the observation of differences in responsiveness to the chemical carcinogen in different stocks of the same strain of rat. The studies of EMF effects on cell cultures were in general consistently negative, with no evidence of genotoxicity or cell transformation.

The most intriguing data in this context come from in vitro studies of the action of weak (1.2 μT) power frequency magnetic fields in blocking the inhibitory effects of melatonin on the growth of human breast cancer cells in culture [Liburdy, et al. 1993]. There is some supporting evidence in terms of independent corroboration [Blackman, et al. 2001; Ishido, et al. 2001], but the effect is found only in a specific sub-clone of one (MCF-7) oestrogen-responsive breast cancer cell line. The Advisory Group concludes that the effect is fairly small, not robust, and has doubtful significance for human health.

Overall, AGNIR conclude that the evidence to date does not support the hypothesis that exposure to power frequency EMFs affects melatonin levels or the risk of breast cancer.

Power Frequency EMFs, Melatonin and Childhood Leukaemia Risk

Henshaw and Reiter explored the hypothesis that the suppression of nocturnal melatonin by power frequency magnetic fields increases the risk of childhood leukaemia [Henshaw and Reiter 2005]. These authors reviewed many of the same experimental and epidemiological studies of the effects of predominantly power frequency magnetic fields on nocturnal melatonin levels as did the UK independent Advisory Group [AGNIR 2006], summarised above. In addition, they consider the evidence for a role of melatonin as a natural anti-oxidant, protecting against radical-mediated DNA damage from reactive oxygen species etc., particularly in human haemopoietic tissue, and speculate on the possible significance of a suppression of nocturnal levels of melatonin on DNA damage and tumour initiation in fetal haemopoiesis. The authors note that initiating events in childhood acute lymphoblastic leukaemia are thought to take place in utero [Greaves 2002].

In their review of the experimental and epidemiological data, Henshaw and Reiter draw attention to the many positive outcomes reporting a suppression of nocturnal melatonin levels in response to power frequency magnetic field exposure. The authors also note the lack of effect seen in many volunteer studies, but comment on the many drawbacks to such studies, including the small numbers of volunteers that participate, the short exposure periods and the absence of features such as transients that might normally be encountered in everyday life. Greater weight is placed on the outcome of the occupational and residential studies and on the three longest-term volunteer studies, namely [Wilson, et al. 1990], [Wood, et al. 1998] and [Graham, et al. 2000]. They conclude that, overall, eleven studies lend support for melatonin disruption, assayed principally from measures of the

excretion of a major metabolite of melatonin, by power frequency magnetic fields. Following a discussion of the anti-oxidant properties of melatonin, and of possible mechanisms for EMF effects on melatonin production in the pineal and on circulating melatonin the authors draw attention to the possibility that weak power frequency magnetic fields may be able to increase free radical concentration through effects on radical-mediated metabolic reactions, se for example [Brocklehurst 2002].

Henshaw and Reiter conclude that the hypothesis that power frequency magnetic fields may cause an increased risk of childhood leukaemia via decreased melatonin levels is plausible but note that key aspects remain to be tested. Thus, the authors have presented essentially a hypothesis generating paper. However, both groups, AGNIR 2006 and Henshaw and Reiter 2005, recognised the need for further research.

Emerging Biological Technologies Relevant to EMF Research

A number of high throughput screening technologies have emerged over the past decade that have considerably advanced our ability to detect the biological effects of various environmental agents such as electromagnetic fields (EMFs) on biological systems. The various strengths and weaknesses of these technologies as applied to EMF health effects research have been discussed at a Workshop held in Helsinki in 2005; see [Leszczynski 2006; Leszczynski and Meltz 2006].

The weak nature of EMF interactions at the molecular level has suggested that biological effects are unlikely to result from genotoxic or mutational changes to the genome itself but more probably through what are sometimes termed epigenetic[1] changes. These new technologies provide the means whereby both qualitative and quantitative information regarding gene expression and the ensuing metabolic activity of the transcribed proteins can now be rapidly assessed. Automation provides the means for greatly increasing the amount of information that may be derived from a single experiment but at a cost, namely the increased difficulty in identifying biologically significant responses from the experimental 'noise'. Increasing reliance is placed on sophisticated analytical software packages but, at the end of the day, some verification is usually required from other established techniques, ideally from another laboratory.

Genomics is a broad term covering the study of the genome of an organism, including DNA sequencing of the genome and comparative genomics, which looks at genome differences between species. In EMF research, for the reasons given above, it is probably more appropriate to investigate functional changes. Transcriptomics, sometimes called functional genomics, describes the study of gene expression; the genome in human and other mammalian cells comprising typically up to 20,000 – 30,000 genes. The transcriptome comprises the RNAs produced from the genome of a cell or tissue. For various technical reasons, prior to analysis, RNA is converted back to the complementary DNA (cDNA) sequences using reverse transcriptase. Techniques using oligonucleotide chips or cDNA glass microarrays rely on the binding of fluorescence labelled cDNA from the cells of interest to a set of complementary sequences on the chip or array and measuring the fluorescence intensity at each site. In this way the quantitative measures of gene ex-

[1] Epigenetics is more conventionally defined as reversible heritable changes in gene function that occur without a change in the DNA sequence of the genome, as occurs in the main through DNA methylation or histone acetylation.

pression within the entire genome in cells from two populations can be compared. Interpretation of the results however relies heavily on complex statistical analysis that is very sensitive to the applied level of stringency with which meaningful responses are identified; see [Mayo, et al. 2006]. In addition, it is widely acknowledged that there is a need to verify any ensuing changes in gene expression through other techniques such as quantitative PCR. Alternative sensitive techniques becoming available include HICEP (high coverage gene expression profile) in which all RNA transcripts are amplified and separated by capillary electrophoresis for subsequent sequencing.

Proteomics is the term applied to the global analysis of the protein complement of a cell. This can be influenced by a variety of factors including post-translational modification. Typically, analysis is by 2D gel electrophoresis, greatly improved in recent years by the development of standardised protocols and sophisticated image analysis software. Various mass spectrometry techniques such as MALDI-TOF (matrix assisted laser desorption/ionisation time-of-flight mass spectrometry) can be used to identify individual proteins. In addition, protein microarrays and chips, often based on monoclonal antibodies, are being developed that will provide quantitative information regarding the expression of a series of functionally linked proteins. These techniques can also be applied to measure the functional state of proteins by examining their phosphorylation status.

Metabolomics is the third in this group of mass screening technologies that have emerged over the past decade or so and is applied to the profiling of metabolites within an organism. With each increased level of complexity from gene expression through to metabolite profile, interpretation becomes more difficult, suggesting that the application of metabolomics to EMF studies might at present be somewhat premature.

The various strengths and pitfalls of some of these high throughput technologies for screening for EMF-induced 'epigenetic' changes in experimental studies are discussed in detail by [Leszczynski and Meltz 2006] in their rapporteurs' report of the Helsinki Workshop. These authors concluded that the techniques are at present useful primarily as experimental research tools. However, they may eventually be used to identify endpoints suitable for screening for animal, volunteer and epidemiological investigation, leading to a better understanding of the potential health effects, if any, of environmental levels of EMF exposure.

Update on key issues

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

The possibility that some individuals are particularly sensitive and react with symptoms to exposure to EMF has been discussed in a previous report [IEGEMF 2004] 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 [IEGEMF 2006 (current report)]. While these symptoms are very real and some subjects suffer severely, there are hardly any data that suggest that EMF exposure is a causal factor.

The few studies that have been published on health risks among populations living near transmitters have had major methodological shortcomings [IEGEMF 2003; IEGEMF 2005; IEGEMF 2006 (current report)]. 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 [IEGEMF 2003]. 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.

Studies of cancer risk in mobile phone users have been discussed in all reports [IEGEMF 2003; IEGEMF 2004; IEGEMF 2005; IEGEMF 2006 (current report)]. 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.

For power frequency fields only few studies have been published in recent years which has been discussed in several reports [IEGEMF 2004; IEGEMF 2005; IEGEMF 2006 (current report)], and the previous assessment by IARC remains unchanged, namely that ELF magnetic fields are a possible human carcinogen. WHO recommend in its recently finalized ELF Environmental Health Criteria document (not yet published) that implementing very low cost precautionary procedures to reduce exposure is reasonable and warranted.

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 [IEGEMF 2005].

Research on interaction mechanisms in both ELF and RF ranges is moderately active. The most plausible model for ELF (and static) effect is that of the radical pair which may have seen some confirmation in some of the bird navigation investigations, but is unlikely to be applicable to humans. By contrast, there is no plausible model yet for RF nonthermal mechanisms [IEGEMF 2006 (current report)].

Research priorities

Important research needs remain within all frequencies of EMF as identified by the WHO EMF programme and more recently by EMF-NET and by SCENIHR (European Commission Scientific Committee). One reason is that new technologies are spread rapidly which results in increased exposure to the population from various frequencies within the EMF range. The Swedish Government has announced plans to provide an additional 10 million SEK for research administered by the SSI. Even though this funding will have to cover research within all areas of radiation protection, the SSI has pointed out EMF as a prioritized area. The IEG looks very positively at this and suggests that SSI specifies that a certain proportion of the available funds will indeed be used for EMF research.

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SSI report

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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