SSI report

SSI Rapport
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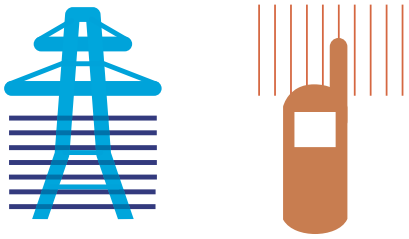
Reports from SSI:s International Independent Expert Group on Electromagnetic Fields 2003 and 2004



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.

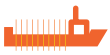
Health care
The second largest contribution to the total radiation dose to the Swedish population comes from health care. SSI is working to reduce the radiation dose to employees and patients through its regulations and its inspection activities.

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.

AUTHOR/ FÖRFATTARE: SSI's Independent Expert Group on Electromagnetic Fields/ SSI:s vetenskapliga råd för elektromagnetiska fält.

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

TITLE/ TITEL: Reports from SSI's International Independent Expert Group on Electromagnetic Fields 2003 and 2004.

Part 1: Recent Research on Mobile Telephony and Cancer and Other Selected Biological Effects – First Annual Report from SSI's International Independent Expert Group on Electromagnetic Fields, 2003

Part 2: Recent Research on Mobile Telephony and Health Risks – Second Annual Report from SSI's International Independent Expert Group on Electromagnetic Fields, 2004

SUMMARY: Part 1: The focus of the 2003 report is on epidemiological and experimental cancer research, blood-brain barrier and heat shock proteins. In none of these areas have there been breakthrough results since the British Stewart-report and the Swedish RALF-report that have warranted firm conclusions in one way or the other.

Part 2: The three first reports from the Interphone Study have been presented this year. A Swedish study suggests that long-term use of mobile phones increases the risk of acoustic neuroma, at the side of the head where the phone is used. The results, however, must be interpreted with caution while other groups with sufficient numbers of long term users finalize their analyses. For ELF magnetic fields there are indications that children might be more sensitive; however, we lack the understanding of how, or even if, these fields might be involved in leukemogenesis. For RF fields, widespread exposure to these fields is recent and very little is known about the potential sensitivity of children.

SAMMANFATTNING: Del 1: I korthet anser SSI:s vetenskapliga råd för elektromagnetiska fält och hälsa att inga nya genomgripande resultat kommit fram under de senaste tre åren som förändrar nuvarande riskbedömningar inom de områden som diskuteras. Slutsatserna från bl.a. den engelska Stewart-rapporten och den svenska RALF-rapporten gäller i allt väsentligt fortfarande. I 2003 års rapport diskuterar rådet bl. a. epidemiologisk och experimentell cancerforskning, studier av blod-hjärnbarriären och påverkan på "heat shock proteins".

Del 2: Under 2004 har de tre första studierna som ingår i INTERPHONE-projektet presenterats. INTERPHONE är en stor internationell studie av samband mellan användning av mobiltelefon och olika typer av hjärntumörer. En svensk delstudie påvisar en förhöjd risk för tumör på hörselnerven vid långvarig användning av mobiltelefon (mer än tio år). SSI:s vetenskapliga råd diskuterar också barns känslighet för elektromagnetiska fält.

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The conclusions and viewpoints presented in the report are those of the authors and do not necessarily coincide with those of the SSI.

Författarna svarar själva för innehållet i rapporten.

Statens strålskyddsinstitut
Swedish Radiation Protection Authority

Sammanfattning

Del 1: I korthet anser SSI:s vetenskapliga råd för elektromagnetiska fält och hälsa i sin rapport för 2003 att inga nya genomgripande resultat kommit fram under de senaste tre åren som förändrar nuvarande riskbedömningar inom de områden som diskuteras. Slutsatserna från bl.a. den engelska Stewart-rapporten och den svenska RALF-rapporten gäller i allt väsentligt fortfarande. Rådet konstaterar att ett intensivt forskningsarbete pågår i många länder och att ny kunskap successivt kommer att bli tillgänglig. Forskningsområdet är komplicerat och det är väsentligt att forskningsresultat kan upprepas av andra forskargrupper innan de accepteras. Den snabba teknikutvecklingen gör att det är viktigt att följa upp olika typer av tänkbara hälsoeffekter redan på ett tidigt stadium, eftersom det kan ta lång tid att upptäcka skador i form av t.ex. cancer eller kroniska sjukdomar. Rådet understryker därför vikten av fortsatt forskning inom EMF-området.

Del 2. Under 2004 har de tre första studierna som ingår i INTERPHONE-projektet presenterats. INTERPHONE är en stor internationell studie av samband mellan användning av mobiltelefon och olika typer av hjärntumörer. En svensk delstudie påvisar en förhöjd risk för tumör på hörselnerven vid långvarig användning av mobiltelefon (mer än tio år). SSI:s vetenskapliga råd menar att resultaten måste tolkas med försiktighet och övriga delstudier med lång användningstid inväntas innan några säkra slutsatser kan dras. Inga samband mellan kortare användning av mobiltelefon och hörselnervstumörer kunde påvisas och inte heller några samband mellan mobiltelefonanvändning och andra typer av hjärntumörer. WHO arrangerade i början av sommaren en konferens om barns känslighet för elektromagnetiska fält. För extremt lågfrekventa fält finns indikationer på att barn skulle kunna vara mer känsliga, men det saknas kunskap om hur, eller ens om, sådana fält skulle kunna orsaka t.ex. leukemi. För radiofrekventa fält saknas till stor del relevanta undersökningar. SSI:s vetenskapliga råd menar att även om det inte finns några observerade effekter går det inte heller att säga att exponeringen är ofarlig för barn, särskilt med tanke på att studier på barn i stort sett saknas. I det sammanhanget påpekar expertgruppen att den stödjer den försiktighetsattityd som SSI intagit både för extremt lågfrekventa fält och för användning av mobiltelefoner. Det vetenskapliga rådet har också utvärderat REFLEX-studien som orsakat en del tidningsskriver under hösten. REFLEX är ett EU-projekt där 12 olika laboratorier undersökt effekter på olika typer av cellkulturer vid låga exponeringar av elektromagnetiska fält. Rådet noterar att några laboratorier rapporterat DNA-skador för relativt låga nivåer av elektromagnetiska fält, både extremt lågfrekventa och radiofrekventa. Alla studier har dock ännu inte publicerats i vetenskapliga tidskrifter. Rådet konstaterar också att fynden av DNA-skador står i motsägelse till tidigare forskningsresultat och måste kunna upprepas av ytterligare forskningsgrupper innan slutsatser kan dras.

Summary

Part 1: The focus of the 2003 report is on epidemiological and experimental cancer research, blood-brain barrier and heat shock proteins. In none of these areas have there been breakthrough results that have warranted firm conclusions in one way or the other. It is worth noting, however, that intense research is currently ongoing in several countries and new data will gradually become available. Given the complexity of the research area it is essential that both positive and negative results be replicated before accepted. Given the increase of new technologies, it is essential to follow various possible health effects from the very beginning, particularly since such effects may be detected only after a long duration, due to the prolonged latency period of many chronic diseases. Thus, more research is needed to address long-term exposure, as well as diseases other than those included in the ongoing case-control studies.

Part 2: For radiofrequency (RF) exposure the number of studies on symptoms available today is too small to allow conclusions. For extremely low frequency (ELF) fields quite a number of studies have been performed. In none of these studies have subjects been able to detect fields at levels at which they claim to react. Recent results on RF exposure and cognitive functions have not clarified the picture. Recent investigations on humans and animals have not added clear evidence of alteration of EEG and/or sleep. While new data have not provided evidence that memory of rodents is affected by exposure to RF fields, the data are still inconclusive in humans but possible effects do not seem to be detrimental. The three first reports from the Interphone Study have been presented this year. A Swedish study suggests that long-term use of mobile phones increases the risk of acoustic neuroma, at the side of the head where the phone is used. The results, however, must be interpreted with caution while other groups with sufficient numbers of long term users finalize their analyses. Physical, chemical and therapeutic agents have the potential for affecting development, depending on the nature of the agent and the timing and magnitude of the exposure. For ELF magnetic fields there are indications that children might be more sensitive; however, we lack the understanding of how, or even if, these fields might be involved in leukemogenesis. For RF fields, widespread exposure to these fields is recent and very little is known about the potential sensitivity of children. Given the paucity of data indicating a particular vulnerability of children to EMF, it may be tempting to conclude that children are not more susceptible than adults to RF exposure. However, the absence of an observed effect does not necessarily mean that exposure is harmless, especially if crucial studies focusing on children are yet to be done. Given scientific uncertainty SSI has adopted precautionary approaches for both ELF and RF, which we endorse.

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Part 1. Recent Research on Mobile Telephony and Cancer and Other Selected Biological Effects – First Annual Report from SSI's International Independent Expert Group on Electromagnetic Fields, 2003

Preface

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

The composition of the group for the period of 2002-2004 is:

Prof. Anders Ahlbom, Karolinska Institutet, Stockholm, Sweden (chairman);
Prof. Jukka Juutilainen, University of Kuopio, Kuopio, Finland;
Dr. Bernard Veyret, University of Bordeaux, Pessac, France;
Dr. Harri Vainio, IARC, Lyon, France (currently Occupational Health Institute, Helsinki, Finland);
Prof. Leeka Kheifets, WHO, Geneva, Switzerland (currently UCLA, Los Angeles, USA);
Dr. Eduard David, University of Witten/Herdecke, Witten, Germany;
Prof. J. Malcolm Harrington, London, UK.

Ass. Prof. (Docent) Maria Feychting, Karolinska Institutet, has been appointed scientific secretary to the group.

Stockholm in December 2003
Anders Ahlbom
Chairman

Executive summary

This is the first annual report by an international independent expert group for electromagnetic fields and health appointed by SSI. The scope of this first report is radio frequency fields of the type used by mobile telephony. The group decided to focus on epidemiological research on cancer and exposure from mobile phones and transmitters as well as experimental cancer research. In addition three selected topics were also discussed, namely blood-brain barrier, heat shock proteins, and precautionary framework. A review (IEGMP 2000) commissioned by the UK government was used as starting point.[1]

Tumours in mobile phone users

Only a small number of epidemiological studies on mobile phone use and cancer risk are available. Overall, the majority of the studies have found no indication of increased risks, although some positive findings are reported in two studies. There are, however, methodological considerations that limit the interpretability of these few positive findings. Limitations are also obvious in the studies that are reporting no effects, primarily because of short follow-up periods. Thus, current evidence is inconclusive regarding cancer risk following RF exposure from mobile phones.

Tumours in people living near transmitters

The research on potential effects of exposure to radiofrequency fields emitted by transmitter towers is at a very early stage of development. Several methodological problems, including exposure assessment, have resulted in data that are difficult to interpret. It seems that a prerequisite for a new generation of informative studies is the introduction of a personal exposure meter that can be used in epidemiological studies.

Carcinogenicity

Recent animal studies have not provided evidence that RF radiation similar to that emitted by mobile phones could induce cancer or enhance the effects of known carcinogens. The open questions include repeatability of one earlier positive finding, relevance of the experimental models used, and effects at higher exposure levels. These questions will probably be answered by ongoing and planned animal carcinogenicity studies. In experiments with cells, genotoxic effects (increased micronuclei and aneuploidy) were reported in two studies at exposure levels higher than those found in the tissues of mobile phone users. There is no consistent evidence for effects relevant to non-genotoxic mechanisms of carcinogenesis, such as cell proliferation and apoptosis, or for induction or enhancement of neoplastic transformation *in vitro*.

Heat shock proteins

In recent years several articles have described effects of radiofrequency signals on the expression of stress proteins (heat shock proteins, HSP) *in vitro* and *in vivo*. These HSP

[1] Stewart report

act to prevent or repair protein alteration due to stress. These observations were done at low exposure level and a direct effect of temperature elevation can be excluded. There are many confirmation studies in progress and it is presently not possible to conclude about the existence and the mechanism of these effects and even less about relevant health consequences. However, this is an important area for research as HSP expression might be used as a marker of RF exposure.

Blood brain barrier

The permeability of the blood-brain-barrier, which protects the brain against toxins circulating in the blood vessels, has been studied in animals exposed to RF. In most cases, an increase in permeability was seen only at high SAR levels related to temperature increases of the tissues. However, two research groups, in France and Sweden, have reported leakage of the blood-brain-barrier at low to medium SAR levels. In the work of the Swedish group, damage was still present in the brain of rats, 50 days after a 2-hour exposure to mobile telephone signals. Overall, results published or communicated on the BBB have drawn a lot of attention but a careful analysis of the available data does not indicate the existence of a health risk. However, further work in this area must be performed.

Precautionary framework

Given that scientific uncertainty reflected in this report will remain at least in the near future, WHO has been developing a precautionary framework that would allow for the development of reasonable policies in the face of uncertainty. This framework advocates precautionary thinking at all stages of issue management, while emphasizing the importance of proportional response based on the consideration of cost effectiveness, risk trade off, and benefit cost calculations.

Conclusion

The focus of this report is on epidemiological and experimental cancer research, blood-brain barrier and heat shock proteins. In none of these areas have there been breakthrough results that have warranted firm conclusions in one way or the other. It is worth noting, however, that intense research is currently ongoing in several countries and new data will gradually become available. Given the complexity of the research area it is essential that both positive and negative results be replicated before accepted. Given the increase of new technologies, it is essential to follow various possible health effects from the very beginning, particularly since such effects may be detected only after a long duration, due to the prolonged latency period of many chronic diseases. Thus, more research is needed to address long-term exposure, as well as diseases other than those included in the ongoing case-control studies.

Introduction

The Independent Expert Group (IEG) decided that the scope of this first report would be radio frequency fields (RF), i.e., such electromagnetic fields that are used for example in connection with mobile telephony. The Stewart report was taken as starting point for this work (IEGMP 2000). This report was commissioned by the UK government and published in 2000 and is a comprehensive review of available scientific data at that time. As a consequence, the present evaluation looks at results that have been made available in 2000 and onwards. The group has not attempted to comment on every single study but has chosen for review some areas that have been judged to be of particular importance for scientific reasons or because of significant public attention and visibility.

Since most of the epidemiological studies on tumours in phone users have been published after the Stewart report was presented, they are reviewed here. Some of the epidemiological research on populations living near transmitters is also reviewed here. In vivo and in vitro carcinogenicity studies have been considered as central and, hence, an assessment of this literature has been included in the report. Other topics of high interest that have been included are heat shock proteins and blood-brain-barrier damage. Finally the group has included a discussion on the so called precautionary framework that is based on work being done at WHO, Geneva. A discussion on research on electrical hypersensitivity and other research on EMF and symptoms will be covered in next year's report.

It has been recognized by the group that an issue of considerable public concern and of great relevance is whether or not children are particularly sensitive to a possible health effect from EMF exposure. However, the group concluded that virtually no data are directly available on which to base an assessment of this issue. The group also noted that this is a topic that currently is receiving quite substantial attention by various organizations and researchers internationally and that at least one scientific meeting will be devoted to this subject during 2004. The group therefore decided to postpone a discussion of this important topic for next year's report when the basis for an assessment is assumed to be better.

Tumours in mobile phone users

Brain tumours

To date, only a small number of epidemiological studies on mobile phone use and cancer risk exist; the majority of these studies focus on brain tumour and acoustic neuroma (Table 1) but some study other tumour types (Table 2).

The first case-control study of brain tumours was conducted in Sweden (reported in three publications: Hardell et al. 1999; 2000; 2001), and included cases diagnosed in two regions in Sweden and still alive when recruited to the study, and two controls per case matched for sex, age, and regional population register (Table 1). Details of mobile phone use were gathered by self-completed postal questionnaires complemented by a telephone interview (Hardell et al. 1999). High participation rates were reported in the publication, but in fact only about one third of the total number of malignant brain tumour cases in the population was included (Ahlbom & Feychting 1999), probably because many cases had died before they were approached by the investigators. The response rate in controls was

remarkably high for a population based study. There was no overall association of phone use with brain tumours or acoustic neuroma, nor was there any association with analogue or digital phone use considered together or separately, whether for 1, 5 or 10 years latency periods, and no dose-response or significant laterality effects were seen. Subsequent reanalysis of the same data by laterality (side of phone use versus side of tumour occurrence) showed an association of borderline significance with temporal, temporoparietal and occipital tumours combined (Hardell et al, 2001) for lateral tumours. Since there was also a risk reduction at other locations, recall bias is an obvious candidate for explaining these results. While a population-based study should have avoided the selection biases inherent in other study designs, this was not so in this study of prevalent living cases.

Muscat et al have conducted two case-control studies in the USA, one of malignant brain tumours (Muscat et al 2000), and the other of acoustic neuroma (Muscat et al, 2002), using the same ascertainment and data collection procedures. Cases (469) were identified at participating hospitals, and controls (422) were selected from the same hospitals frequency matched on age, sex, race and month of admission, with a variety of malignant and benign conditions. Information about mobile phone use was obtained by standard interviews (proxies were interviewed for 9% of cases and 1% of controls). No raised risks were seen for regular use, frequency of use, or duration of use, or for site or histologic subtype of brain cancer (an excess of tumours on the side of phone use for cerebral tumours overall ($p = 0.06$) was reversed for temporal lobe tumours ($p = 0.33$)). In the second study, 90 patients with acoustic neuroma were compared with 86 controls. There was no trend in risk of acoustic neuroma in relation to cumulative measures of phone use, and no significant relation between side of phone use and side of tumour. The studies are limited by the short duration of mobile phone use among the majority of subjects and the hospital based identification of cases and selection of controls from other patient groups at the hospitals.

In another case-control study in the USA (Inskip et al. 2001), interview data were obtained from 782 cases with malignant or benign brain tumours, treated at participating hospitals. Most of the cases were interviewed within three weeks after diagnosis. Controls (n=799) were admitted to the same hospitals as the cases with non-malignant conditions matched for age, sex, race, and proximity of residence to hospital. Proxies were interviewed for 16% of patients with glioma, 8% with meningioma, 3% with acoustic neuroma and 3% of controls. Results adjusted for potential confounding variables showed no link between cumulative use of mobile phones (mainly analogue) and risk of brain tumour overall or according to histological subtype or anatomic site and side of use. No increased risks were found for acoustic neuroma. Longer use ($\geq$5 years) or early start of use ($\leq$1992) were not associated with increased risks. This study suffers from the same limitations as the studies by Muscat et al. described above, i.e. hospital based design and too few subjects that have used mobile phones for an extended time period.

A Danish cohort study (Johansen et al. 2001) included 420,095 cellular network subscribers (80% of all private subscribers in Denmark), 31% of whom had begun subscriptions in 1993 or earlier. The cohort constituted approximately 10% of the adult Danish population, and was followed from first subscription through 1996. Cancer incidence in the cohort was ascertained by linkage to the Danish Cancer Registry with average follow-up for analogue and digital subscribers being 3.5 and 1.9 years respectively. Standardised incidence ratios comparing cancer incidence in phone users (mostly digital) with national rates allowing for sex, age and period, showed reduced risk of cancer overall (SIR = 0.89, 95% CI: 0.86–0.92), and of brain and nervous system tumours (SIR = 0.95, 95%

CI: 0.81–1.21). Risks did not vary by time since first subscription, age at first subscription, use of analogue versus digital telephones, duration of digital phone use, anatomical location or histology of brain tumours. Acoustic neuroma was not analysed separately. The study has limited power to study long-term effects of mobile phone use; only 8% of the cohort was followed at least 6 years. Twenty-four brain and nervous system tumour cases had used a mobile phone 5 years or longer; the risk estimate in this category being 1.0 (95% CI: 0.7-1.6). The registry based design guarantees exposure information of similar quality for all subjects in the cohort, regardless of disease, and is independent of the subjects' ability to remember their mobile phone use. However, relying on private cellular network subscription as a proxy for mobile phone use results in substantial non-differential misclassification of the exposure, since the actual user of the phone is unknown. Not being able to include corporate users, likely to be among the earliest and heaviest users of mobile phones, also weakens the statistical power of the study. Furthermore, the entire exposed cohort is included in the national incidence rates. However, the study covers a period when mobile phones were still used by a minority of the population and the resulting exposure misclassification would only be able to completely hide a very small risk increase.

A register-based case-control study was conducted in Finland (Auvinen et al, 2002). All people diagnosed with brain tumours in 1996 aged 20 to 69 years were ascertained from the National Cancer Registry and 5 age- and sex-matched controls per case were drawn from the national population register. Subscription records of national network providers provided the index of exposure to mobile phones. The average duration of subscription was 2-3 years for analogue phones and less than 1 year for digital. There was no information available about the frequency or duration of calls or about use of cell phones provided by an employer. The odds ratio (OR) for brain tumours with ever-subscription was 1.3; for glioma 1.5 (95% CI: 1.0-2.4) (null for other brain tumour histologies). Analogue phone use gave an OR of 2.1 (95% CI: 1.3-3.4) for glioma and digital phone use an OR of 1.0. Acoustic neuroma was not analysed separately. An increased risk of glioma was found already after 1-2 years duration of subscription to an analogue phone. Adjustment for place of residence, occupation and socio-economic status did not alter the findings. As in the Danish cohort study, assessing exposure as private mobile phone subscribers leads to considerable misclassification of the exposure. However, this type of bias cannot explain the increased risks observed. The strength of this approach to exposure assessment is that recall bias is avoided. However, an increased risk of glioma after only 1-2 years of subscription to an analogue mobile phone seems unlikely both because of the short duration of the exposure and the very short latency between exposure and cancer occurrence. If it was true, it should have been observed also in the Danish cohort study that has a similar approach to exposure assessment, and most likely also in all the other case-control studies available. Furthermore, considering the rapid increase of mobile phone use in the general population during the last decade (from a few percent to over 80%), a doubling of the risk of glioma after 1-2 years of mobile phone use should be visible in incidence trends based on cancer registry data. However, there is no indication of increased incidence of glioma in the age groups where mobile phone use is common (Lönn et al., in press).

A second Swedish case-control study was conducted by Hardell et al. (reported in three publications: 2002a, 2002b, 2003), including cases of brain tumour ascertained 1997 - 2000, and alive at the time of recruitment to the study. One control per case, matched for age, sex and region, was selected from population registers. Information on exposure to

cellular and cordless phones was collected through mailed questionnaires and completed over the phone, similarly to the first study. Excluding cases with erroneous diagnoses (e.g. metastasis or wrong diagnosis date) left 2253 available cases of which 1303 were included in the study (58%). Results for all brain tumour types combined are driven by the acoustic neuroma results; no associations were found between mobile phone use and malignant brain tumours, or benign brain tumours other than acoustic neuroma. An increased risk of 3.5 (95% CI: 1.8-6.8) was found for acoustic neuroma among users of analogue mobile phones, whereas results for digital phones were close to unity. For other tumours located in the temporal lobe (where all acoustic neuromas are located) an increased risk of meningioma was indicated among users of analogue phones. However, the highest risk seems to be for meningioma cases with a short latency of mobile phone use (within 5 years). Sub-analyses with different latent periods showed no coherent patterns for any tumour types. There were no adjustments for confounding variables beyond adjustment for use of other types of mobile phones, and matching variables. The study has a limited power to study effects of long-term use of digital phones. It is noteworthy that the prevalence of mobile phone use had not increased much between the first and second Swedish study; the increase in the proportion of users among controls was at the most 6%. Between 1996 and 2000 mobile phone use in the general Swedish population increased from 28% to 71%. These estimates are based on number of subscriptions in the total Swedish population, and may be an overestimate because some persons have multiple subscriptions. However, multiple subscriptions cannot account for the entire difference in the increase in proportion of users. As in the first Swedish study (Hardell et al. 1999), the long delay between diagnosis and case recruitment tend to lead to loss of high-grade tumours.

In further analyses of malignant brain tumours in the same material (Hardell et al. 2002b), increased risks were reported for ipsilateral use of mobile phones, although with no coherent pattern with latency periods or amount of use. Furthermore, reduced risks for contralateral use were also found. For example, the risk for malignant brain tumours associated with ipsilateral use of an analogue mobile phone was 1.85 (95% CI: 1.16-2.96) whereas the risk for contralateral use was 0.62 (95% CI: 0.35-1.11). A similar pattern was found for use of digital phones. These analyses were adjusted for socio-economic status.

In a third paper based on the same material, the authors reported results for which the matching was ignored, and the exposure definition changed (Hardell et al. 2003a). In the first reports, each telephone type was analysed separately; in this third paper, the unexposed group was defined as those that had no exposure to any type of mobile or cordless telephone. Generally, results were similar to the two previous papers, except that the reduced risks for contralateral use had disappeared, and there appeared to be a relation with latency, which was not seen previously. Matching variables were only partially controlled for (age and sex, but not geographical region). As results of matched analyses with the new exposure definition were not presented or discussed, there is no possibility to assess the impact on the results of ignoring the matching (if any).

Other tumours

No association was seen with parotid gland tumours in the Finnish case-control study, based on 34 cases, of which only 4 were exposed (Auvinen et al, 2002), or in the Danish cohort study (7 exposed cases) (Johansen et al. 2001). The small sample size is a severe limitation in both studies.

A mixed population and hospital-based case-control study of uveal melanoma (Stang et al. 2001) included 118 cases and 475 controls. Occupational exposure to mobile phones for several hours a day for 6 months or more assessed by interview gave a raised OR (4.2, 95% CI: 1.2-14.5), reflecting the hospital-based participants (OR = 10.1, based on 5 exposed cases and 1 exposed control). The low participation rate among the population based controls (48%) and the partly hospital based study design make selection bias a potential source of bias in the study. The study is also limited by the small number of exposed subjects.

The risk of ocular melanoma was assessed in the Danish cohort study (Johansen et al. 2002). No association with mobile phone use was observed, based on 8 exposed cases. The authors also report a stable incidence of ocular melanoma in Denmark from 1943-96.

Finally, the risk of leukaemia and various other types of cancers were assessed in the Danish cohort study (Johansen et al. 2001), but no relation with phone use was found.

Discussion and conclusions

Handheld mobile phones were first introduced in the late 1980s, but were not used by many until the 1990s. Given that cancer is induced several years after exposure to carcinogens and an additional number of years elapse before medium /low grade tumours are clinically detectable, then, *a priori,* cancer risk cannot be properly evaluated among users of mobile phones until after a certain amount of time. This is even more pronounced for slow-growing benign tumours like acoustic neuroma. None of the available studies has enough power to study the effect of long-term mobile phone use on the risk of developing specific types of brain tumours or other cancers. This is particularly relevant because the vast majority of the available results are negative.

Apart from limited statistical power, bias of different sorts may affect the studies. The amount of selection bias is difficult to evaluate in the hospital based case-control studies. These studies rely on the assumption that other patients at the hospital correctly reflect the habits of mobile phone use in the population from which the cases had come. In population based studies this is usually a smaller problem. However, in some of the studies reported here, the included cases constitute a selected group that have survived long enough to be recruited to the study; if survival time is in any way related to the exposure (directly or indirectly), this may introduce bias. The register based studies do not have problems with selection bias.

Differential recall of mobile phone use among those with and without a cerebral tumour in case-control studies is another major source of bias, which could lead to overestimated risks; indeed some evidence of this was discussed above. However, reporting bias is also likely since presence of a brain tumour may distort both memory and hearing, which in turn could lead to underestimated risks. Relying on private cellular network subscription as a proxy for mobile phone use does not lead to a systematic difference between cases and non-cases, and therefore risk estimates would not be biased away from the null. However, it would have resulted in non-differential misclassification since subscribers and users are not the same (Funch et al, 1996); corporate users, likely to be among the earliest and heaviest users of mobile phones, were excluded in the studies that used this approach.

Overall, while occasional significant associations between various brain tumours and analogue mobile phone use have emerged, no single association has been consistently reported across population-based studies. The few positive findings reported in two of the studies are difficult to interpret; they are either based on small numbers, have too short latency periods to be credible, or emerged only after a series of re-analyses that are reported in such a way that they are difficult to follow. Also the remarkably high response rates (about 90% for the controls) in the Swedish study limit the interpretability of these findings. At the same time, for reasons discussed above, the negative results of most of the studies cannot be taken as evidence against an effect either. Thus, current evidence is inconclusive regarding cancer risk following RF exposure from mobile phones. There are currently several epidemiological studies of mobile phone use and head- and neck tumours underway, as part of a large international collaboration coordinated by the International Agency for Research on Cancer (WHO's cancer research institute). Hopefully, these will shed more light on this issue. However, given the increase of new mobile phone technologies, it is essential to follow various possible health effects from the very beginning, particularly since such effects may be detected only after a long duration, due to the prolonged latency period of many chronic diseases. Thus, research is needed to address long-term exposure, as well as diseases other than those included in the ongoing case-control studies.

Tumours in people living near transmitters

To date all studies on environmental exposure and tumours are based on radio and TV antennas; no studies around mobile phones and base stations have been published yet. One could argue that since the exposure from base stations and radio and TV transmitters is several orders of magnitude below that from the phones, exposure from transmitters would not be a concern. However, transmitters give rise to extended exposure to the whole body and during longer time periods; it also differs from that of the phones in that it is involuntary. Thus, there are good reasons to study also mobile phone base stations and other transmitters.

The Stewart report concluded after thorough review of the studies on populations living in the vicinity of transmitters that these studies to date have major limitations, which weaken the conclusions that can be drawn from them. Perhaps the most pronounced problem with the studies is that distance from a broadcasting tower has been taken as a proxy for exposure, but no account has been taken of ground reflections and signal reduction by buildings, vegetation and undulations.

Since the Stewart report, we are only aware of one other study on cancer to have been published in the scientific literature and that is a study based on the population leaving near the Vatican Radio Station (Michelozzi et al. 2002). The Vatican Radio station is a very powerful station that transmits all over the world and people living in the neighbourhood have been concerned about possible health effects and have demanded an epidemiologic investigation in the population residing around the transmitters. The station consists of numerous transmitters with transmission powers ranging from 5 to 600 kW, and different frequency bands (nine transmitters for short waves with frequencies of 4,500-21,850 kHz, and three transmitters for medium waves, with frequencies of 527-1,611 kHz). This study looked at leukaemia mortality in adults and leukaemia incidence in children in the population living within a 10 km radius circle of the centre of the transmitters. The authors divided the circle in 2 km wide bands to allow for trend analyses using

Stone's test for decreasing rates with increasing distance. In adults and with both genders taken together the SMR within 2 km was 1.8 (95% CI: 0.3-5.5) based on 2 cases. Stone's test gave a p-value of 0.14. The excess risk and the trend were essentially confined to males. In children the SMR for those living within the 2 km radius circle was 6.1 (95% CI: 0.4-27.5) based on one case. Elevated SMRs were observed for all cumulative bands up to 10 km but all had wide confidence intervals and the total number of cases within the 10 km radius circle was 8. The Stone test for trend was reported as p=0.004. No systematic EMF measurements were made in the area and the epidemiologic analyses were based on the assumption that distance from the sources can serve as a proxy for exposure. The numbers of cases were small in particular for children, which precludes firm conclusions. For adults, the results are somewhat inconsistent in that the risk elevations are mainly confined to males.

In one of the earlier studies on people living near transmitters an attempt was made to assess the power density at various locations within the affected municipalities (Hocking et al. 1996). It was concluded that at the centre the power density was approximately 1 $\mu W/cm^2$, with the maximum within the area being about 8 $\mu W/cm^2$ at roughly 2 km from the centre. At 4 km they calculate the power density to be 0.2 $\mu W/cm^2$. This illustrates the difficulty with using distance from the source as a proxy for exposure[2].

The research on exposures to radiofrequency fields from transmitter towers and cancer is clearly at a very early stage of development. Diverse exposure sources, poorly estimated population exposures, small numbers of cases, and selective investigation (because several studies were conducted in response to neighbourhood concerns) and quite possibly selective publication, have resulted in data that are difficult to interpret. Therefore, suggestions of a possible link of distance to leukaemia in some studies (Hocking et al. 1996; 1998; Michelozzi et al. 2002) need confirmation in further research before conclusions about effects of RF exposure can be drawn.

It seems that a prerequisite for a new generation of informative studies to emerge is the introduction of a RF meter that can be used in large scale epidemiological research. It is a strong recommendation that the development of such an instrumentation is supported in any possible way. With such a meter available this might be a high priority research area.

Cancer-related in vivo and in vitro studies

Carcinogenicity in animals

Long-term animal carcinogenicity studies have a key role in providing evidence for the carcinogenicity of chemical and physical agents. The standard test has traditionally been two-year rodent bioassays, in which the animals are exposed only to the agent being tested. Because there are carcinogens that are apparently not carcinogenic alone, experimental models have also been developed for testing combined effects with known carcinogens. The Stewart report (IEGMP 2000) reviewed studies published before 2000, and concluded that animal cancer studies *"have provided equivocal evidence for an effect on tumour incidence."* Studies published after the Stewart report are reviewed here.

[2] The values given in $\mu W/cm^2$ correspond to 10, 80, and 2 mW/m^2, respectively.

RF exposure alone, without exposures to known carcinogens

The findings of Repacholi et al. (Repacholi et al., 1997) were considered in the Stewart report as the most positive evidence for cancer-related effects of mobile phone-type RF radiation in animals. A two-fold lymphoma incidence was reported in animals exposed to RF radiation for 1 h/day. Transgenic Eμ-*Pim1* mice were used in this study. These animals are predisposed to develop lymphoma and thus provide a sensitized model to test for cancer. The weaknesses of this study included incomplete histopathology and large uncertainty in dosimetry (0.008 – 4.2 W/kg). The relevance for human health of the transgenic model is also less well characterized than that of traditional two-year animal bioassays. Utteridge et al. (2002) conducted a replication of the Repacholi study. In this study, both Eμ-*Pim1* and wild-type (nontransgenic) animals and four RF exposure levels (0.25 to 4.0 W/kg) were used [information on how good the dosimetry was is yet to be published], with 120 animals per group. No significant effects were found. There were some differences from the protocol of the Repacholi et al. study: the animals were restrained, they were exposed only once per day for 1 h in the morning, on 5 days per week (In Repacholi's study, unrestrained animals were exposed two times for 30 min in the morning and in the evening, 7 days per week). The biological relevance of these differences is unclear, but the comparability of the two studies have been questioned based on the differences, as well as other aspects of the Utteridge study, (Kundi, 2003; Lerchl, 2003; Goldstein et al. 2003a,b). Additional replication studies are ongoing.

La Regina et al. (2003) performed a two-year carcinogenicity study using F344 rats. Eighty female and 80 male rats per group were exposed to one of two mobile phone signals (FDMA or CDMA) or sham-exposed. The rats were exposed 4 h/d, 5 days per week, and the brain SAR was 1.3 W/kg. No significant differences were found between the exposed and sham-exposed animals for any tumour in any organ.

RF exposure combined with known carcinogens

The most common experimental protocols for testing co-carcinogenic effects (combined effects with known carcinogens) are based on the concepts of "initiation" and "promotion". An initiator is an agent that causes DNA damage and thus initiates the carcinogenic process by giving rise to potential cancer cells carrying mutations in cancer-related genes. A promoter is a subsequent exposure that enhances the development of the mutated cells into a tumour (the third and last step of carcinogenesis, "progression", then leads towards increased malignancy and metastasis). Promoters are typically non-genotoxic carcinogens (they do not cause DNA damage). The initiation-promotion experimental protocol consists of a single or short-term initial exposure to the selected initiator, followed by repeated application of the agent being tested for its promoting action.

The initiation-promotion model is not adequate for describing the complex multi-step process of carcinogenesis, or real-life human exposure to a cocktail of simultaneous exposures (Juutilainen et al., 2000). To reveal co-carcinogens that are not "promoters", other protocols may be needed, such as the "photo co-carcinogenesis" studies (Forbes and Sambuco, 1998) that involves repeated long-term exposure to UV radiation together with long-term exposure of the skin to the chemical being tested.

Heikkinen et al. (2001) used ionising radiation as an initiator and tested mobile-phone type 900 MHz radiation as a possible promoter. Female CBA/S mice, 50 animals per

group, were exposed to ionising radiation in the beginning of the study and then to RF radiation for 1.5 h per day, 5 days a week for 78 weeks. One group was exposed to a continuous NMT-type RF field at a whole-body average SAR of 1.5 W/kg and another group to a pulse-modulated GSM-type field at 0.35 W/kg. The carcinogenic action of ionising radiation was at the desired moderate level - clear and statistically significant, but not too strong so that it would have masked any promoting effects. For example, lymphoma was observed in 24% of the animals exposed to ionising radiation, compared to no lymphomas found in the control animals. RF exposures did not cause significant further increase of lymphoma or any neoplastic lesion. The incidence of all primary malignant neoplasms pooled was slightly higher in the RF-exposed animals, but the difference from animals exposed only to ionising radiation was not statistically significant. Overall, the results of this study did not provide evidence for cancer promotion by RF radiation.

Two recent studies have investigated possible promoting effects of mobile-phone type RF radiation on rat mammary tumours initiated by 7,12-dimethylbenz(a)anthracene (DMBA). Bartsch et al. (2001) conducted three independent experiments on Sprague-Dawley rats exposed to an initial dose of DMBA and continuously to GSM-modulated 900 MHz RF fields. The whole-body average SAR was 17.5-70 mW/kg. In the first experiment, median time to the development of the first malignant tumour in each animal was significantly longer in the exposed group than in the sham-exposed group. However, this finding was not confirmed in the two later experiments with the same protocol. Overall, the study did not demonstrate any significant differences between the groups in tumour latency or incidence. The same experimental model (Sprague-Dawley rats and DMBA) was used by Anane et al. (2003), but the exposure levels were higher, and the animals were exposed only 2 h/d, 5 days per week. The RF field exposures started 10 days after the DMBA treatment. In the first of two independent experiments, 16 rats were sham-exposed and three groups of 16 rats were exposed to whole-body average SARs of 3.5, 2.2 or 1.4 W/kg. In the second experiment, the SAR levels were 1.4, 0.7 and 0.1 W/kg. In the first experiment, the development of tumours was statistically significantly accelerated at 1.4 and 2.2 W/kg but not at 3.5 W/kg compared to the sham-exposed group. In the second experiment, there were no differences in tumour appearance between the two lower exposure levels and the sham-exposed group, but tumours appeared significantly later in the 1.4 W/kg group. Multiplicity of tumours was not significantly increased by the exposures (in the second experiment, the number of tumours per tumour-bearing animal was significantly decreased at 1.4 W/kg). Overall, there were no consistent effects on latency, incidence, multiplicity or tumour volume. Other studies using the DMBA-induced mammary tumour model are ongoing.

In contrast to the above studies, Heikkinen et al. (2003) used a study design not based on the initiation-promotion concept. The known carcinogen was UV radiation, delivered 3 days/week during 52 weeks, and two digital mobile phone signals (GSM at 902.4 MHz and the North American DAMPS at 849 MHz) were tested for possible co-carcinogenic effects. Both RF exposures were delivered 1.5 h/day on 5 days/week, and the whole-body specific absorption rate was 0.5 W/kg. Transgenic female mice over-expressing human ornithine decarboxylase (ODC) gene and their non-transgenic littermates (45 to 49 animals per exposure group) were used. The UV exposure resulted in development of macroscopic skin tumours in 11.5 % and 36.8 % of non-transgenic and transgenic animals, respectively. The RF exposures did not affect tumour development statistically significantly. However, both RF exposures were associated with slightly accelerated skin tu-

mour development (especially in the non-transgenic animals), which may warrant further evaluation.

Genotoxic effects

The association between cancer and genotoxicity is well known. For example, the carcinogenic effects of ionising radiation, UV radiation and many chemical carcinogens is based on their ability to cause DNA damage and consequent gene mutations. Genotoxicity of RF radiation has been tested in many studies both in animals and *in vitro*. Some of these studies have evaluated also possible combined effects with known DNA-damaging agents. Concerning studies published before 2000, the Stewart report concluded: "*Several different assays of genotoxicity have failed to produce clear evidence that RF radiation is genotoxic at non-thermal levels. The most consistent results come from micronucleus formation, but these are not simple to interpret and have uncertain implications for health.*" Four studies published after the Stewart report found no effects on DNA damage, chromosomal aberrations or micronuclei in human peripheral blood lymphocytes or in rat peripheral blood or bone marrow cells exposed to two mobile phone signals (CDMA at 847.74 MHz , FDMA at 835.62 MHz) or to2.45 GHz microwaves (Vijayalaxmi et al., 2000; Vijayalaxmi et al., 2001c; Vijayalaxmi et al., 2001a; Vijayalaxmi et al., 2001b). Two recent studies are reviewed below.

Tice et al. (2002) exposed human blood cells to RF fields using analog or two different digital (CDMA, TDMA) mobile phone signals at 837 MHz, or a digital (GSM) phone signal at 1909.8 MHz. The cells were exposed for 3 or 24 h at specific absorption rates of 1.0-10.0 W/kg. The temperature of the cultures was kept at 37°C by controlling the temperature of the exposure chamber. DNA damage was evaluated in leukocytes using the alkaline single cell electrophoresis ("comet") assay. Chromosomal damage was assessed in lymphocytes mitogenically stimulated to divide post exposure using the cytochalasin B-binucleate cell micronucleus assay. No increased DNA damage was observed in the comet assays. Micronuclei were not increased in leukocytes exposed for 3 hours, but exposure for 24 h at 5 or 10 W/kg resulted in a significant increase in the frequency of micronucleated lymphocytes. The magnitude of the effect was about 4-fold, and all four signals produced a similar response. This is a well-conducted study, and the results appear to be reproducible within the same laboratory. The biological relevance of the positive micronucleus finding is uncertain. Micronuclei can originate either from chromosome fragments (indicating damage to DNA) or from loss of whole chromosomes. Differentiation between these two mechanisms (by using a centromere-specific probe) was not done in this study. The effect was observed at relatively high SAR, and a thermal mechanism remains a possible explanation for the increased micronuclei. There is no obvious explanation for the difference between these results and those of Vijayalaxmi et al. (2001a,b), who found no increase of micronuclei in human lymphocytes using similar methods and similar mobile phone signals at maximum levels of 5 or 5.5 W/kg. Inaccuracies in dosimetry might explain the difference, if there is a threshold for this effect near 5 W/kg.

Mashevich et al. (2003) exposed human peripheral lymphocytes to continuous wave 830 MHz RF fields. The cells were exposed for 72 h using specific absorption rates of 1.6-8.8 W/kg. Heating by the RF fields was compensated by lowering the incubator temperature. Aneuploidy (loss or gain of chromosomes) was assessed by using a fluorescence in situ hybridization probe for detecting the centromere of chromosome 17. An increase

of chromosome 17 aneuploidy was observed as a function of increasing exposure levels. The increase was about 100% at 8 W/kg, whereas no increase was seen at 2 W/kg. The effect was statistically significant at levels exceeding approximately 3 W/kg. The increased aneuploidy was accompanied by increased frequency of asynchronous replication of repetitive DNA arrays associated with the centromere – the same research group has previously reported that such changes are associated with aneuploidy and cancer. In separate additional experiments, aneuploidy was not found to increase with increasing temperature between 34.5°C and 38.5°C. Temperatures of 40-41°C produced an 80% increase of aneuploidy. Because the average temperature of the medium never exceeded 38°C during RF exposure, the authors concluded that the RF effect was nonthermal. The biological implications of the findings are not clear. While aneuploidy seems to be associated with cancer and genomic instability (Duesberg et al., 2000), its causal role in carcinogenesis is controversial.

Non-genotoxic cancer-related effects

The term "non-genotoxic carcinogen" is used for agents that do not cause direct DNA damage, but are nevertheless causally related to cancer. Many non-genotoxic carcinogens are co-carcinogens or "promoters" that act together with genotoxic carcinogens to increase the probability of cancer. The mechanisms of non-genotoxic carcinogenesis are poorly known, and there is no well-established standard test for detecting non-genotoxic carcinogens. Some recent findings and their relevance to non-genotoxic carcinogenesis are discussed below.

Effects on cell proliferation

There is no doubt that increased cell proliferation is important for the process of carcinogenesis, and many known tumour promoters are able to stimulate cell proliferation. According to the Stewart report, studies published before 2000 "*do not demonstrate convincing, consistent changes in cell proliferation under conditions that mimic emissions from mobile phones or base stations.*" No studies published after 2000 were identified. The Stewart report also reviewed studies on ornithine decarboxylase (ODC) activity *in vitro*. ODC is a key enzyme in the synthesis of polyamines. Its activity is elevated in rapidly growing cells (e.g., cancer cells), and it can be considered a marker of cell proliferation. Several known tumour promoters increase ODC activity. The Stewart report concluded: "*Pulse-modulated RF fields from mobile phones may cause a slight increase in ODC levels and activity, at non-thermal levels. However, it is very unlikely that these small changes could…have a tumour-promoting effect.*" Desta et al. (2003) exposed murine L929 fibroblasts to a 835 MHz TDMA-modulated RF field at SARs from <1 W/kg to 15 W/kg. No statistically significant differences between exposed and sham-exposed cells were found at low SAR values. At SARs high enough to cause measurable heating, a dose-dependent decrease of ODC activity was observed. Heating without RF radiation caused a similar decrease. Thus, this study did not confirm the previously reported RF-field-induced increase of ODC activity *in vitro*. Two recent studies have evaluated ODC or polyamine levels *in vivo*. Stagg et al. (2001) did not find effects on ODC activity, in brain tissue of rats after acute exposure (2 hours) to pulsed 1.6 GHz field (Iridium signal) at 0.16, 1.6 or 5 W/kg. In the carcinogenicity study described above (Heikkinen et al., 2003) no changes were observed in skin polyamine levels after chronic exposure (2 years) of mice.

Effects on apoptosis

Apoptosis (programmed cell death) is an important protection mechanism in multicellular organisms: potential cancer cells are removed by apoptosis. Agents that decrease the ability of cells to perform apoptosis will increase the probability that mutated cells survive. Many known tumour promoters have been shown to inhibit apoptosis. Few studies have investigated effects of RF fields on apoptosis. Markkanen et al. (2003) studied combined effects of UV radiation and R F radiation on apoptosis in a mutant yeast (*Saccharomyces cerevisiae*) strain that shows an apoptotic response to elevated temperature. As expected, apoptosis was increased by UV radiation. RF radiation alone had no effect, but combined exposure to GSM-type pulse-modulated RF field and UV radiation resulted in significantly increased apoptosis compared to UV alone. The RF effect was seen at two exposure levels (0.4 and 3 W/kg), and it was dependent on the presence of pulse modulation – continuous-wave fields at identical specific absorption rates had no significant effects on apoptosis. These results suggest effects on the regulation of an important cellular protection mechanism, but the relevance of this finding to human cancer is unknown. Apoptosis in yeast is a newly described phenomenon, and may be different from apoptosis of mammalian cells. Moreover, while suppression of apoptosis might indicate a carcinogenic influence, the increased apoptosis reported in this study is much more difficult to interpret. Studies on the effects of RF radiation on apoptosis in mammalian cells are in progress.

Neoplastic transformation *in vitro*

Transformation assays are *in vitro* models for testing carcinogenic effects and measure the transformation of cultured cells into a more malignant phenotype. Such models have been demonstrated to respond to many known carcinogens and can be used also for studying the combined effects of genotoxic and non-genotoxic exposures. The Stewart report reviewed three studies on neoplastic transformation. In two studies by one research group, 2.45 GHz RF radiation was found to potentiate the transforming effect of X-rays or benzo[a]pyrene in C3H 10T1/2 cells, but only in the presence of the tumour promoter TPA (Balcer-Kubiczek and Harrison 1985; 1991). In the third study, no effects of 836.55 MHz fields were found on neoplastic transformation (Cain et al. 1997). In a more recent study, the C3H 10T1/2 cell transformation assay was used to test the effects of two different mobile phone signals (FDMA at 835.62 MHz and CDMA at 847.74 MHz) at a specific absorption rate of 0.6 W/kg (Roti Roti et al., 2001). The cells were exposed to RF fields alone for 7 days, or first irradiated with X-rays and then exposed to RF fields for 42 days. No statistically significant effects of RF exposures were observed.

Conclusions

Long-term animal cancer studies have in general not provided evidence that RF radiation could induce cancer or enhance the effects of known carcinogens. However, the completed studies might not have included exposure groups with sufficiently high exposure levels. More data on high exposure levels would be helpful for a complete evaluation. The significance of the suggestive positive finding on transgenic animals remains open, and the experimental models used may not have been sufficient for covering all aspects of co-carcinogenic effects. These questions will probably be answered by ongoing or planned animal studies.

Some experimental studies have reported genotoxic effects of RF radiation, but the findings are not consistent. The recently reported increased micronuclei and aneuploidy were observed at exposure levels higher than those found in the tissues of mobile phone users. Given the relatively narrow margin between worst-case human exposures and the levels needed for these effects, further research in this area is warranted.

Concerning effects relevant to non-genotoxic mechanisms of cancer, there is no consistent evidence of effects on cell proliferation at low RF exposure levels. Effects on apoptosis have been evaluated only in one study (more studies are ongoing). The few studies using *in vitro* transformation assays have not provided consistent evidence that RF field exposure could induce or enhance neoplastic transformation.

Heat shock proteins and mobile telephony

The Stewart report discussed studies on gene expression from the perspective of cellular stress response, and concluded: *"While there is currently little evidence that exposure to mobile phone radiation causes a stress response in mammalian cells, judged by elevated gene expression, the results on nematode worms are indicative of non-thermal influence on gene expression."* They referred to the findings on de Pomerai and colleagues, who found increased expression of a heat shock gene in worms exposed to low levels of RF fields [de Pomerai et al., 2000].

Since then, several articles have been published on the potential effects of mobile telephony microwaves on processes involving heat shock proteins (HSP). This is a rather new area of research within bioelectromagnetics. Various stress factors such as excess temperature cause alterations of protein conformation (unfolding, denaturation or aggregation). Since the biological function of a protein is highly dependent upon its structure, stress affects the function of proteins. The HSP are acting as chaperones to facilitate the refolding of altered proteins. They also have a function at key regulatory points in the control of apoptosis (programmed cell death) and chaperones have thus been implicated in the control of cell growth. Discovered in 1962, HSP are classified mainly on the basis of their size (HSP 110, 90, 70 and small HSP). For example, HSP 110 and 70 confer heat resistance to the cell by preventing aggregation and maintaining the folded structure. Elevated levels of HSP are thus indicators of the presence of stress. This is why they have been monitored as potential markers of RF exposure.

In vivo studies

An early and transitory induction of hsp27 ARNm had been observed in the brain of rats locally exposed to RF (900 MHz, CW, 4-hour exposure) with a SAR threshold of 7.5 W/kg (Fritze et al., 1997a).

As stated above, the group of de Pomerai in England published a short article describing results obtained on small worms called nematodes (*Caenorhabditis elegans*) exposed to low-level microwaves (de Pomerai et al., 2000). The endpoint of the assay was the indirect detection of hsp expressed following exposure. The authors had developed transgenic nematodes in order to follow the production of hsp16. In terms of hsp expression, the transgenic worms behaved as if they had been heated by 3°C with respect to controls, and this could not be accounted for by microwave exposure at a low level (ca. 10^{-3} W/kg). Further investigation by the same group led to the publication of results on the growth

and maturation of the nematodes (de Pomerai et al., 2002): they observed identical hsp16 increases in the larvae of worms exposed at 10^{-3} W/kg during 20 hours at 25°C and in sham-exposed larvae maintained at 28°C. Moreover, growth of exposed larvae was 18% faster than that of shams and maturation towards the adult stage increased by 28-40%. These two biological parameters decreased when larvae were kept at 28°C. According to the authors, these observations bring evidence of a nonthermal effect of the microwaves. Further work done *in vitro* by the same authors addressed the mechanism of the observed effects (see below). Replication studies of the data of the de Pomerai group by other research teams are likely to be undertaken soon.

Using a very different approach, the group of Litovitz (Di Carlo et al., 2002) first studied the levels of HSP70 and the resistance to hypoxia in chick embryos exposed to RF (915 MHz, 1.7 W/kg). On the basis of their previous work on 60-Hz magnetic fields, they studied the effects of repeated exposures during incubation (one 20-60-min exposure/day for 4 days). The tested hypothesis was that an acute exposure induces the expression of HSP70, thereby protecting the embryo from hypoxia, while repeated exposures saturate HSP and thus increase sensitivity to hypoxia. The authors indeed showed that acute exposures decreased resistance to hypoxia by 27% and, in a subsequent paper, that acute exposures led to an increase in HSP expression (Shallom et al., 2002). Based on these two sets of data, they speculated that human health could be affected by daily exposure to a mobile telephone in terms of cancer and Alzheimer pathologies, via an oxidative stress mechanism. However, this speculation is not based on a rigorous set of data.

In vitro

An increase in expression and phosphorylation of the Hsp27 protein in human endothelial cells[3] (GSM-900, 2 W/kg, 1-hour exposure) was published by Leszczynski et al. (2002).

In Australia, Laurence et al. (2000) studied the effects of pulsed microwaves on the induction of HSP70 response in murine cells. Short bursts of 2450-MHz microwaves induced an increase of HSP70 with the dose (12-58 W/kg). The authors made some theoretical hypotheses based on these data (see below).

In another study on human cells (MO54 glioma), there was no alteration of Hsp70 following exposure at 2450 MHz (2-16-hour exposures, 5 and 20 W/kg; Tian et al., 2002). In the same study, HSP expression increased at 50 and 100 W/kg to a level beyond that expected from the resulting temperature elevation.

Mechanisms

Laurence et al. (2000) did some theoretical modelling to address the mechanistic issue related to their biological observation (see above). They estimated a cooling time constant of one nanosecond for a 10-nm diameter protein absorbing the microwaves, while protein unfolding occurs on a 50-nanosecond time scale. A hypothesis of theirs is that the power "window" phenomenon, in which biological effects are observed at various low power levels, may be caused by an incomplete triggering of the heat shock response. Little evidence is given by the authors to support such a mechanism.

[3] EA.hy926 cell line

Recently, De Pomerai et al. (2003) have performed some interesting experiments and made some hypotheses. They showed that exposure to low-level microwave radiation (15-20 mW/kg) enhanced the aggregation of bovine serum albumin in vitro in a time- and temperature-dependent manner. It also promoted amyloid fibril formation by bovine insulin at 60°C. They also showed that heat-shock responses were suppressed using RNA interference. They concluded that HSP response to microwaves is probably triggered by conformational alteration to cellular proteins.

Conclusion

The expression of HSP at levels below the thermal threshold has not been confirmed yet. *In vivo* the threshold may be around 7 W/kg. Even if positive results at low level are replicated *in vivo* on nematodes, assessment of the effects of long-term exposure on animals and the health consequences for humans is still required.

Experiments on HSP in cells have yielded inconsistent results, depending on SAR level, laboratory, and type of cells. Several research groups are currently working on various cellular models and exposure regimen.

In conclusion, the need for further research on the potential effects of microwaves on HSP is obvious, even if there is no evidence yet of any detrimental health effect related to HSP processes but these molecules might be shown to be biomarkers of EMF exposure.

Studies on the blood-brain-barrier

One of the most debated issues on the potential bioeffects of mobile telephony signals is that of the results obtained by some research groups on the permeability of the blood-brain-barrier (BBB). This barrier prevents the movement of toxins from the blood into the brain. It is formed by tight junctions in the endothelial cells surrounding the blood vessels. Among the 35 animal and cellular studies published, most of them have shown an increased permeability only at high exposure levels. However, there have been a few publications showing effects at levels close to or below those encountered in mobile telephony. A workshop was recently organised in Germany by FGF and COST 281 to analyse these recent data (www.cost281.org/).

In a paper recently published in the journal Environmental Health Perspectives (EHP), the group of Leif Salford in Lund reported the occurrence of brain damage (permeability of the blood-brain barrier and presence of dark neurons), 50 days after a single whole-body 2-hour exposure of rats to a mobile telephony GSM-900 signal (Salford et al. 2003). This paper has received particular attention in Swedish media and internationally and is thus discussed in some detail here. It follows previous studies by the same group showing increased permeability of the BBB immediately after exposure even at low exposure level (Salford et al. 1994, Persson et al. 1997).

The exposure system was the same that had been used in previous studies by the same group: i.e., GSM-phone-generated signals at 10, 100, and 1000 mW resulting in an estimated whole-body average SAR of 0.002, 0.02, and 0.2 W/kg. No new information is given on the dosimetry of this exposure system, which was set up 10 years ago, despite the fact that numerical and experimental methods have improved much since then.

Sixteen male and 16 female Fischer 344 rats aged 12 - 26 weeks and weighting around 280 g were divided into 4 groups of 8 rats each. Thus, there was a substantial variability with respect to age and weight across the animals. It is also worth noting that the number of animals is small, which limits the possibilities to exclude chance as an explanation for findings. The occurrence of "dark neurons" was judged semi-quantitatively by a neuropathologist 50 days after exposure. Cresyl violet, which was used for that purpose is not known as a specific marker for the identification of degenerative neurons and the number of dark neurons observed may thus be in part the result of staining artefacts and may have been overestimated.

Thus, it is rather puzzling to see a paper in EHP in which information that is so crucial for replication and interpretation of the data is not given. Equally puzzling is to see how the authors fail to put their study in the context of other research and also to draw the far-reaching public health level conclusions. In spite of the limitations in design of the protocol and reporting of the data, it is of utmost importance that the experiment is replicated on a sound basis to ascertain whether effects on the BBB and dark neurons exist following a 2-h exposure to GSM-900. In its recently updated research agenda, WHO (www.who.emf) emphasized that *studies to assess the accuracy and reproducibility of published RF effects on the permeability of the blood-brain barrier and other neuropathologies (e.g., dura mater inflammation, dark neurones) are considered as short-term or urgent needs*. Salford and co-workers are indeed currently doing such a confirmation study. Moreover, data from a replication of the previous results on blood brain barrier damage of the Salford group are underway and should become available soon from a research group at the Brooks Air Force Base in San Antonio, Texas, USA. As for the current results on dark neurons, a multi-centre replication study is planned with five laboratories involved. However, the results will not be available before the end of 2004.

Besides the work of the Salford group, only Aubineau (Töre et al. 2002) in France has reported increased permeability of the BBB following a two-hour exposure with a threshold of a few tenths of W/kg**:** at high and moderate SAR values (2 W/kg and 0.5 W/kg averaged over the brain). GSM microwaves induced permeabilization of intracranial blood vessels, marked in the meninge and discrete in the brain parenchyma, that increased with SAR. Permeabilization was not observed at the lower averaged SAR value presently tested, i.e., 0.18 W/kg. These results have been submitted for publication.

In a long-term experiment, an Australian group reported that prolonged exposure to mobile telephone-type radiation produced negligible disruption to BBB integrity at the light microscope level using endogenous albumin as a vascular tracer (Finnie et al. 2002). Mice had been exposed for one hour per day for 104 weeks at whole-body SAR levels ranging from 0.25 to 4.0 W/kg. In a separate short-term study, the same authors exposed mice for one hour at 4 W/kg and again there was no albumin extravasation (Finnie et al. 2001).

Other negative results had been obtained by Tsurita et al. (2000) who exposed rats to the Japanese mobile telephone signal at 1439 MHz and found no increase in BBB permeability at SAR up to 2 W/kg in the brain in rats exposed for one hour per day during 4 or 8 weeks. The permeability was assessed using Evans blue and immunostaining of serum albumin.

Meanwhile, the Hossmann group in Germany who had found a minor effect at high SAR (around 7.5 W/kg) (Fritze et al. 1997) concluded recently that the neuropathological relevance of an increased BBB permeability is low because even the most pronounced altera-

tions induced by microwave exposure are small compared to established models of BBB disturbances and because BBB changes are quickly reversed (Hossman & Hermann 2003).

The conclusion from the recent workshop on the BBB and RF exposure was that only two groups have reported increased permeability of the BBB at low SAR, while several others have not found such effects (even at high SAR levels). These effects, which need careful replication, have a small amplitude and their consequences in terms of human health are therefore impossible to assess at the present time.

Overall, results published or communicated on the BBB have drawn a lot of attention but a careful analysis of the available data does not indicate the existence of a health risk. However, further work in this area must be performed.

Precautionary framework

Definitions and Goals

The IEG assumes that for the foreseeable future scientific uncertainty will prevail with respect to electromagnetic fields and health. A strategy for dealing with this uncertainty is thus needed. The WHO is currently developing such a strategy, referred to as a precautionary framework. The basic goal of the WHO Precautionary Framework for Public Health Protection (WHO PF) is to respond to health risks before significant harm has occurred. At times, warnings of danger have been ignored and steps to protect the public against preventable deaths, illnesses, and injuries have not been taken, especially when a risk is poorly understood. Even if cause-and-effect relationships cannot be established, protective steps might well be justified.

The idea is to integrate science, economics, psychology, and law into a clear and systematic structure for approaching risks. A general framework cannot, of course, answer every question in advance. But it can discipline analysis by showing:

- how to avoid both inadequate and excessive reactions to risks;
- how to match protective interventions to the existing evidence;
- how to deal with costs and risks of unintended side-effects;
- how to involve stakeholders and the public, enabling ordinary citizens to take protective measures and incorporating social values into precautionary decisions.

The Hierarchy of Responses

Precautionary actions that are proportional to the degree of scientific uncertainty, the severity of possible harm, the size and nature of the affected population, and the cost of the proposed actions should be taken to protect public health. There is a hierarchy of responses, depending on the extent of the anticipated harm. Often, of course, the anticipated harm cannot be specified, and ranges of outcomes are all that can be predicted.

Where the evidence of danger is weak, regulation should usually be avoided, but proportional precautionary measures might still be justified, e.g. personal choice to use a hands-free device. In such cases, continuing research is appropriate to fill gaps in existing knowledge and to ensure that the danger is not larger than current understanding suggests. If the evidence of harm is suggestive, government might disclose the risk to the public or

require product labelling; communication and engagement programmes can be used to assist people to understand the issues and to make their own choices about what to do. In the face of plausible evidence of significant harm, consideration should be given to mitigation and regulatory controls to reduce or to eliminate that harm. Where the evidence of likely harm is strong, limiting exposure and general bans should be considered, certainly if the bans do not create substitute risks or impose costs that exceed likely benefits. In all cases, precautionary measures should be proportional to existing knowledge of the risks.

Evaluating Benefits and Costs

Cost-effectiveness
It is important to identify the most cost-effective precautionary alternative. If there are several means of achieving a precautionary goal, the least expensive and most effective way of doing so should be chosen.

Risk-risk analysis
In all cases, government should understand and attend to the risks sometimes introduced by regulations. If regulations threaten to introduce their own risks, this should be considered in choosing appropriate precautions. Precautionary approaches should be carefully chosen so as not to create new or substitute risks. At the same time, precautionary approaches are especially desirable if they diminish several risks at the same time.

Costs and benefits
To the extent feasible, precautionary approaches should be undertaken after balancing both costs and benefits. If the costs of certain precautionary actions are extremely high, they should be avoided unless there is reason to believe that the risk of harm is also extremely high. If the costs of precautions are low, steps should be taken even if the risk seems very small or uncertain. Prudent precaution will often favour low-cost measures for reducing poorly understood risks.

Conclusions

This first annual report of SSI's independent expert group looks at studies on possible biological effects of radio frequency electromagnetic fields. The focus is on epidemiological and experimental cancer research and on blood-brain barrier damage and heat shock proteins. In none of these areas has there been break through results that have warranted firm conclusions in one way or the other. Indeed, while quite a number of new studies have been published within these areas in recent years, the overall scientific assessment has not changed markedly since the Stewart report was published and the conclusions that were formulated at that time are still to a great extent valid. It is worth noting, however, that intense research is currently ongoing in several countries. This research is often part of a scientific program that has been aimed to fill the gaps in knowledge identified by the WHO EMF Project in order for the WHO to complete its assessment of health risks and electromagnetic fields. Given the complexity of the research area it is essential that both positive and negative results be replicated before accepted. Given the increase of new technologies, it is essential to follow various possible health effects from the very beginning, particularly since such effects may be detected only after a long duration, due to the prolonged latency period of many chronic diseases. Thus, more research is needed to address long-term exposure, as well as diseases other than those included in the ongoing case-control studies.

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Table 1. Results for epidemiological mobile phone studies of brain tumours

	Brain tumours		**Brain tumours, longer latency**		**Acoustic neuroma**	
	No. exp cases	RR (95% CI)	No. exp cases	RR (95% CI)	No. exp cases	RR (95% CI)
Hardell et al, 1999, 2000, 2001	78	1.0 (0.7-1.4)	34 16	0.8 (0.5-1.4) >5 yr 1.2 (0.6-2.6) >10 yr	5	0.8 (0.1-4.2)
Muscat et al, 2000, 2002	66	0.8 (0.6-1.2)	17	0.7 (0.4-1.49 ≥4 yr	11	1.7 (0.5-5.1)
Inskip et al, 2001	139	0.8 (0.6-1.1)	22	0.7 (0.4-1.4) ≥5 yr	22	1.0 (0.5-1.9)
Johansen et al, 2001	154	1.0 (0.8-1.1)	24	1.0 (0.7-1.6) >5 yr	Not analysed separately	
Auvinen et al, 2002	40 analogue 16 digital	1.3 (0.9-1.8)	18	1.5 (0.9-2.5) >2 yr	Not analysed separately	
Hardell et al, 2002a, 2002b, 2003	188* analogue 224* digital	1.3 (1.0-1.6) 1.0 (0.8-1.2)	120* analogue 46* analogue 33* digital	1.1 (0.8-1.6) >5 yr 1.3 (0.8-2.3) >10 yr 0.9 (0.6-1.5)	38* analogue 23* digital	3.5 (1.8-6.8) 1.2 (0.7-2.2)

* Discordant pairs

Table 2. Basic data and results for epidemiological mobile phone studies of other tumours

	Study population	**Tumour type (numbers cases/ controls)**	**RR (95% CI)**	**% users among controls**	**Reported response rate cases/controls**
Johansen et al, 2001, 2002 Cohort	Denmark. Nationwide cohort study. Private cellular network subscribers, 1982-95. Cases: ≥18 years. Incidence in cohort compared to national incidence 1982-96.	Salivary gland tumours (7) Leukaemia (84) Ocular melanoma (8)	0.8 (0.3-1.6) 1.0 (0.8-1.2) 0.6 (0.3-1.2)	10% of general adult population (*private subscribers)*	Register based
Auvinen et al, 2002 Case-control	Finland. Nationwide, 1996. Cases: 20-69 yr, Controls: National population register.	Salivary gland (34/170)	1.3 (0.4-4.7)	<11% (*private sub-scribers*	Register based
Stang el al. Case-control	*Population based:* Four regions in Germany 1995-97. Cases: 35-69 yr. Controls: Selected from mandatory lists of residence *Hospital based:* One region in Germany 1996-98. Cases: 35-74 yr. Controls: patients with benign disease of posterior eye segment, excl. occupational accidents.	Uveal melanoma (37/699) Uveal melanoma (81/148)	1.6 (0.0-16.5) 10.1 (1.1-484.5)	6.4% (*at least six months several hours per day)* 2.7% (*at least six months several hours per day)*	84/48 % 88/79 %

Note: when % users are given as less than a value it is estimated as the sum of the users of analogue and digital phones respectively, not taking into account that a person could have used both an analogue and a digital phone.

Part 2. Recent Research on Mobile Telephony and Health Risks – Second Annual Report from SSI's International Independent Expert Group on Electromagnetic Fields, 2004

Preface

The Swedish radiation protection agency, SSI (Statens strålskyddsinstitut) has appointed an international independent expert group (IEG) for electromagnetic fields (EMF) and health. The task is to follow and evaluate the scientific development and to give advice to the SSI. The IEG will take recent major scientific reviews as starting points and in a series of annual reports consecutively discuss and assess relevant new data and put these in the context of already available information. The result will be a gradually developing 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 second annual report.

The composition of the group for the period of 2002-2004 has been:

Prof. Anders Ahlbom, Karolinska Institutet and Stockholm Center for Public Health, Sweden (chairman);
Prof. Jukka Juutilainen, University of Kuopio, Kuopio, Finland;
Dr. Bernard Veyret, University of Bordeaux, Pessac, France;
Dr. Harri Vainio, IARC, Lyon, France (currently Occupational Health Institute, Helsinki, Finland);
Prof. Leeka Kheifets, WHO, Geneva, Switzerland (currently UCLA, Los Angeles, USA);
Prof. Eduard David, University of Witten/Herdecke, Witten, Germany;
Prof. J. Malcolm Harrington, London, UK. (Resigned in August 2004)

Ass. Prof. (Docent) Maria Feychting, Karolinska Institutet, has been appointed scientific secretary to the group.

Stockholm in December 2004
Anders Ahlbom
Chairman

Executive Summary

Symptoms

For RF exposure the number of studies available today is too small to allow conclusions as to whether such fields can cause various symptoms. For ELF fields the situation is different: quite a number of studies have been performed. In none of these studies have subjects been able to detect fields at levels that are comparable to those at which they claim to react. So far no study has been able to prove a link between ELF- EMF and the occurrence of symptoms. Therefore, the IEG suggests that the term “electromagnetic hypersensitivity” should not be used.

Cognitive functions/neurophysiology

Recent results on RF exposure and cognitive functions have not clarified the picture. Changes in cognitive functions have been reported but, as stated in a previous review, the results are inconsistent and no single clear effect on cognitive function can be identified. The new results on ELF fields have not provided any information that would alter the conclusions of the previous reviews (the earlier positive studies generally used stronger fields).

EEG and sleep

Recent investigations on humans and animals have not added clear evidence of alteration of EEG and/or sleep. In any case, the relevance of minor alterations on EEG and sleep on health is not significant.

Memory

While new data have not provided evidence that memory of rodents is affected by exposure to RF fields, the data are still inconclusive in humans but possible effects do not seem to be detrimental.

National results from the Interphone Study

The three first reports from the Interphone Study have been presented this year. A Swedish study suggests that long term use of mobile phones increases the risk of acoustic neuroma, at the side of the head where the phone is used. The results, however, must be interpreted with caution while other groups with sufficient numbers of long term users finalize their analyses. Both this study and a Danish study reports no effect on acoustic neuroma for short term use (The Danish study has fewer long term users). For brain tumors the Swedish study does not indicate any association with mobile phone use, for short term or long term use or for any specific tumor site.

Combined effects of electromagnetic fields with environmental carcinogens (CEMFEC)

Based on the results of the animal study, cocarcinogenic effects of RF fields are not likely in this experimental model and at the exposure levels chosen. This conclusion is supported by the fact that no enhancement of in vivo genotoxic effects were found and by the fact that in vitro studies did not show enhancement of the effects of the two chemicals or any effects characteristic to non-genotoxic carcinogenesis.

Exposure of children to RF and ELF fields

Physical, chemical and therapeutic agents have the potential for affecting development, depending on the nature of the agent and the timing and magnitude of the exposure. For ELF magnetic fields there are indications that children might be more sensitive; however, we lack the understanding of how, or even if, these fields might be involved in leukemogenesis.

Widespread exposure to these fields is recent and very little is known about the potential sensitivity of children to RF fields. Given the paucity of data indicating a particular vulnerability of children to EMF, it may be tempting to conclude that children are not more susceptible than adults to RF exposure. However, the absence of an observed effect does not necessarily mean that exposure is harmless, especially if crucial studies focusing on children are yet to be done. Given scientific uncertainty SSI has adopted precautionary approaches for both ELF and RF which we endorse.

Introduction

The 2003 annual report of the IEG focused on RF and in particular epidemiological studies on cancer, as well as on studies on experimental carcinogenicity, heat shock proteins, and blood brain barrier effects [Swedish Radiation Protection Authority 2003]. The IEG noted in all these sections that there were various open questions but also that current research was addressing these issues attempting to confirm or replicate previous results or by looking at complementary aspects. The plan for the IEG is to revisit each of these issues when new data are available and to update the discussion and conclusions. This year we report on some new epidemiologic data, but for the other issues too little new data have emerged and further discussions of these topics will have to wait.

This annual report brings up a set of different issues. We first review the literature on a widely discussed topic, namely whether exposure to fields increases the frequency of asthenic symptoms either in a susceptible group of the population or in the general population; this is often referred to as electrical hypersensitivity. Somewhat linked to this is the possibility of cognitive effects and neurophysiological effects from EMF exposure and we review this as well as studies on EEG and sleep and memory in the present report. As in 2003, the starting point is the Stewart report from 2000 [IEGMP 2000] and the update of the Stewart report made in 2003 by NRPB's independent Advisory Group on Non-Ionising Radiation (AGNIR) [NRPB 2003]. Several European research programs have come to, or are about to come to, an end and we have included a summary and discussion of the main results of some of these programs. It is in this context we discuss some recent epidemiological data that have come out of the Interphone Study. The extent to which children might be extra sensitive to electromagnetic fields was touched upon in the previous year's report but was postponed till this year primarily to include the discussion of the WHO-conference on this topic which was held during the summer of 2004. In this context we also discuss exposure policy for children. A starting point for this discussion is IARCs classification of ELF-EMF in Group 2B "possible carcinogen to humans".

Symptoms

Background

The term ”electromagnetic hypersensitivity” (EHS) if often used to denote a phenomenon where individuals experience adverse health effects while using or being in the vicinity of electric, magnetic, or electromagnetic field sources and devices, and when the individuals themselves attribute their symptoms to these sources and devices. There are no diagnostic criteria available, and symptoms experienced vary substantially between different individuals, but are generally non-specific with no objective signs present. The severity of the condition varies; the majority of cases present mild symptoms, but some cases experience severe problems with major consequences for work and everyday life. The scientific literature on this area has been reviewed previously by Bergqvist et al. for the European Commission [Bergqvist, et al. 1997], updated in 2000 [Bergqvist, et al. 2000], and by Levallois [Levallois 2002]. This report briefly summarizes the findings of the previous reviews, and evaluates additional studies available in the scientific literature.

It is difficult or even impossible to correctly estimate the prevalence of EHS, simply because there are no established diagnostic criteria, and the definition of the disease is largely based on each individual’s own beliefs and attribution of various symptoms to different sources of electromagnetic field exposure. Therefore, assessments of the prevalence will entirely depend on the methods used to identify cases, and the types of questions asked in each specific survey. The hitherto reported prevalence of EHS varies considerably throughout the world and between reports; at the time of the review for the European Commission [Bergqvist, et al. 1997] it was most common in the Nordic countries and Germany with less than 1%, but very rare or non-existent in other countries, e.g. the UK and the Netherlands. A cross-sectional survey performed in 1997 on a random sample of the population in Stockholm, Sweden, reported a prevalence of 1.5% [Hillert, et al. 2002], and a survey made on a sample of the general population in California estimated the prevalence to 3.2% [Levallois, et al. 2002]. For reasons discussed above the validity of the reported prevalence in different studies can be questioned, and the prevalence in different countries cannot easily be compared.

Röösli et al. [Roosli, et al. 2004] report results from a Swiss descriptive study of persons complaining about symptoms that they attributed to electromagnetic fields. The most common symptoms were sleep disorders, followed by headaches, nervousness or distress, fatigue and concentration difficulties. The most common sources to which the subjects attributed their symptoms were mobile phone base stations (74%), mobile phones (36%), cordless phones (29%) and power lines (27%).

Surprisingly few etiologic studies have been made on this health problem, and the majority of them have focused on skin symptoms related to video display terminal (VDT) use. The unspecific nature of the disease is a major difficulty in this research, especially because the patient’s attribution of the symptoms to sources of electromagnetic field exposure is an important part of the disease definition.

Studies on “electromagnetic hypersensitivity” can for natural reasons only be made on humans, and the available studies are either epidemiological (observational) or experimental (provocation studies). Most studies have focused on extremely low frequency

(ELF) fields or VDT use, but there are also some studies on radiofrequency (RF) exposure from mobile phones or base stations.

RF exposure and symptoms

Epidemiological studies

To date all of the existing epidemiological studies on RF exposure and symptoms are cross-sectional, which makes them of limited value in an evaluation of whether low level RF exposure can cause various symptoms. In a cross-sectional study the exposure and the outcome are assessed simultaneously, without consideration of the time sequence of the events. In addition, all of the available studies on RF exposure ask the subjects themselves to assess both their exposure (e.g. distance to nearest base station or amount of mobile phone use) and the outcome (various symptoms), which lead to a considerable risk that the exposure assessment is influenced by the disease, or that only symptoms that an individual attribute to the RF exposure are reported. Another limitation is that the participation rates in most of the studies are low or not possible to assess, and there is a large potential for selection bias; people who experience symptoms that they attribute to mobile phones or base stations may be more prone to participate in a study investigating this particular question, than people with no such beliefs. Also the Stewart report [IEGMP 2000] acknowledged the limitations inherited in studies using a cross-sectional design.

At present there are only two studies on base station exposure and symptoms published; one from France [Santini, et al. 2002a] and one from Spain [Navarro, et al. 2003]. None of the studies have reported how subjects were selected for participation in the studies, and participation rates cannot be estimated. Participants have answered questions about various symptoms such as headaches, concentration difficulties, memory loss, fatigue, sleeping problems etc. They were also asked to estimate the distance to the nearest base station, with no independent validation. Not only is self reported distance to base stations a questionable exposure assessment method; it has also been shown that distance is a poor surrogate for RF exposure from base stations [Schuz and Mann 2000]. The Spanish study also made measurements of the exposure in the homes, but did neither report how subjects were selected for measurements nor the proportion of subjects agreeing to have measurements taken in their homes. For unknown reasons they have also excluded all participants living between 150 and 250 meters from a base station, which makes correlation coefficients between distance and exposure of little value. Both the French and the Spanish study report an increased prevalence of symptoms close to base stations, but the design limitations make it impossible to assess whether these findings are a results of bias or real effects.

Three studies have investigated the prevalence of symptoms among mobile phone users [Chia, et al. 2000; Oftedal, et al. 2000; Santini, et al. 2002b], with participation rates varying from 45% to 65%. The study by Oftedal et al. was performed to assess differences between users of analogue and digital phones. Various symptoms were reported among heavy users of mobile phones primarily among participants from Norway and to a lesser degree among participants from Sweden, but did not differ between users of different types of phones. The symptoms reported were a feeling of warmth on, around or behind the ear, headache, dizziness, fatigue, concentration difficulties. The study by Chia et al. reported a somewhat increased prevalence of headaches among mobile phone users, and a lower prevalence of concentration difficulties. None of the other types of symptoms

differed between mobile phone users and others. Santini et al. found no differences in reported symptoms related to mobile phone use. The results vary considerably between studies, and it is possible that the way the study was introduced to participants, how questions where phrased, recent reports in the local media, or differences in participation rates may have influenced the results. These findings cannot be used to draw conclusions about the effect of mobile phone use on the occurrence of various symptoms.

In conclusion, the available epidemiological studies provide little information regarding the question if RF exposure from base stations or mobile phones can cause various symptoms.

Experimental studies

Another approach to test the hypothesis that RF exposure from mobile phones or base stations can cause various symptoms is to perform an experimental study where the exposure circumstances are controlled by the investigator in a so called provocation study. In this type of study the occurrence of symptoms during periods of exposure are compared to the occurrence of symptoms during unexposed periods. The ideal design is a double blind study where neither the investigator nor the subject is aware of when the exposure is on or off, which minimizes the possibility that knowledge about the exposure will influence the assessment of the studied outcome. Many electrically hypersensitive persons claim that their symptoms occur immediately after having been close to for example an active mobile phone, and for this group of EHS persons an experimental study is probably the most valid study design. So far only three provocation studies have been performed on RF exposure and symptoms.

A Finnish research group reported results from two provocation experiments each including 48 healthy subjects [Koivisto, et al. 2001]. In one experiment, subjects were studied during two 60 min sessions 24 hours apart, where half of the subjects were exposed to GSM 900 MHz during the first session and half during the second, and the other study had two 30 min sessions following directly after each other. Subjects where not aware of when the exposure was on or off. No association between the exposure and occurrence of symptoms was found, and generally few symptoms were reported. If only a small proportion of the population are affected by exposure to mobile phones this would not have been detected in this small study of healthy volunteers.

Another Finnish study [Hietanen, et al. 2002] included 20 subjects that were selected because they claimed to be sensitive to exposure from mobile phones. The purpose was to study symptoms occurring in sensitive persons after exposure to RF fields from mobile phones, and to test their ability to detect whether the fields were on or off. The study used a double blind design and reported results from four 30 min sessions 60 min apart: one session with exposure to a 900 MHz analogue mobile phone, one with a 900 MHz digital phone, one with an 1800 MHz digital phone and one with no exposure. Study subjects were asked to report experienced symptoms immediately, and all symptoms that occurred during a session disappeared during the break. The results showed that more symptoms were reported during the sessions without exposure than when the exposure was on. The subjects were unable to detect the presence of the RF field better than chance. A limitation in the study is that the unexposed session always was one of the first two sessions; there are indications that the participants experienced more stress in the beginning of the experiment which may have hampered the ability to discover an association should one exist.

These are the only two available provocation studies of mobile phone use, and both have limitations that prevent conclusions.

A Dutch study of exposures similar to that from mobile phone base stations, the so called TNO-study, included one group of 36 EHS subjects claiming to experience symptoms in connection to GSM mobile telephony and one group with 36 healthy subjects [Zwamborn, et al. 2003]. The groups differed in terms of age and gender distribution and therefore no comparisons could be made between the groups, only within groups for periods with and without exposure. The subjects were exposed to a 1 V/m field at 900 MHz and 1800 MHz (GSM signal), and 2100 MHz (UMTS signal). Each subject participated in three sessions one of which was unexposed, using a double blind design. Each session took 45 min including exposure, questionnaire, and break. The questionnaire estimated degree of well being from 23 assessed symptoms. Both the EHS group and the healthy volunteers reported a somewhat lower degree of well being during UMTS exposure compared to no exposure, whereas no effects were seen for periods of GSM 900 or 1800 exposures in either of the groups. This is the only available study of base station exposures and the results need to be interpreted cautiously, which is also acknowledged by the authors. The results do not explain existing reports of perceived symptoms from base stations since these symptoms are related to the second generation of mobile telephony. Additional studies are needed before any conclusions can be drawn. One such replication study is ongoing in Switzerland; the study protocol is available on the web: www.mobile-research.ethz.ch.

ELF exposure and symptoms

Detailed reviews of these studies can be found elsewhere [Bergqvist, et al. 2000; Bergqvist, et al. 1997; Levallois 2002]. These reviews concluded that some of the epidemiological studies of skin disorders and VDT use report an excess prevalence of subjectively reported symptoms among VDT users, whereas no consistent association was seen between VDT use and objective signs. All of these studies are cross-sectional, and can therefore not be used to assess whether electromagnetic fields from the VDT can cause skin disorders. A study published after these reviews found no differences in magnetic field levels assessed over 24 h between EHS patients and healthy controls [Sandstrom, et al. 2003], but did also use a cross sectional design. The purpose of the study was to describe differences between EHS patients and healthy controls in terms of ECG, heart rate, and heart rate variability, as an indication of a dysbalance in the autonomic nervous system among EHS patients, but with no attempt to determine the cause of any differences.

Several experimental provocation studies have been performed where EHS subjects were exposed in the laboratory to test their ability to detect the electromagnetic fields. The studies used a double-blind crossover design with different exposure settings; one study exposed subjects to either a personal computer (PC) with low fields, or one with high fields ([Swanbeck and Bleeker 1989], one used a PC that was either on or off [Andersson, et al. 1996], one used a filter that reduced the fields from the VDT, a passive filter, or no filter [Oftedal, et al. 1999], and one combined exposure from a VDT with other stressors [Lonne-Rahm, et al. 2000]. Neither in studies of subjects having primarily skin symptoms in connection to VDU work, nor in studies of subjects with a more general electromagnetic hypersensitivity were EHS patients able to detect the fields. Adding additional stressors did not change this picture. Some of these studies exposed subjects in an open session to establish that they did react to the fields, but they could not detect the fields in

subsequent double blind experimental sessions. In some studies, subjects reported symptoms when they believed that the fields were on, but unrelated to the actual exposure. The study of filters for reduction of the fields from the VDT found a significant decrease of symptoms during periods with filters compared to periods with no filter, regardless of whether the filter was active or passive [Oftedal, et al. 1999].

The experimental studies have been criticized for the unnatural experimental situation which may have influenced the subjects' ability to detect the fields. To take this into consideration a Swedish study was performed in the homes or workplaces of EHS subjects [Flodin, et al. 2000], with several days between sessions and a 24 h of follow-up to detect late appearing symptoms. A control group with healthy volunteers was also included. EHS subjects could not better than controls detect exposure to electric and magnetic fields.

Overall conclusions

For ELF fields, quite a number of studies have been performed, and in none of these studies have EHS patients been able to detect electric or magnetic fields at levels that are comparable to those at which they claim to react.

For RF exposure the number of studies available today is too small to allow any conclusions as to whether these fields can cause various symptoms. Several studies are ongoing, and will hopefully report results within the near future.

So far no study has been able to prove a link between electromagnetic fields and the occurrence of symptoms.

Recently a workshop was organized by WHO to review, evaluate, and discuss the scientific evidence related to the question of whether electromagnetic field exposure can cause various symptoms (WHO workshop, Prague, October 2004). At this workshop, no new data was presented that would change the picture described above. It was suggested that the term electromagnetic hypersensitivity should not be used, because of the lack of evidence that EMF exposure plays a role in the occurrence of the symptoms. Instead the term idiopathic environmental intolerance (IEI) was suggested. However, the IEG does not believe that this term is any better. In fact, any term that combines exposure and health will make scientific investigations of etiology more complex. Three working groups were formed at the WHO workshop; one that will work on the definition of the outcome and intervention strategies, one that will discuss communication, and one that will address the need for future studies and research recommendations.

An epidemiological study properly designed to test the hypothesis that electric or magnetic fields can cause various symptoms in a small group of sensitive persons would need to be a very large prospective cohort study with repeated assessment of both the outcome and the exposure, which would be a huge undertaking. As long as experimental studies have not been able to establish that electromagnetic fields can trigger symptoms in EHS patients, such a study cannot be recommended.

Cognitive functions/neurophysiology, RF, ELF

RF fields

"The body of evidence regarding direct RF exposure effects on cognitive function remains inconsistent. Some well-conducted studies have reported significant changes in cognitive functions due to RF exposure, while others have found no significant effects. Among those studies reporting changes, both facilitatory and inhibitory effects of RF exposure have been reported. Overall, no single clear effect of RF exposure on cognitive function can be identified" After the above conclusions by AGNIR (2003), a few studies have been published, and are reviewed here.

Maier et al. [Maier, et al. 2004] exposed 11 volunteers to a GSM-type RF field from a programmable cellular phone held 4 cm from the left ear (unknown whether 900 or 1800 MHz). An auditory discrimination task was applied and participant's current 'Order Threshold' (OT) value was determined. The OT was defined as the minimum time needed to a) recognize that two auditory stimuli are presented just separately and b) to decide without error on what side the first of both stimuli was presented. Following a first test cycle, the volunteers had to relax for 50 min while being, or not being, exposed to pulsed electromagnetic fields. Subsequently, the test was repeated. Neither the participants nor the experimenter were aware of when the exposure was on or off. Data acquired before and after the resting phase were compared from both experimental conditions. Nine of the 11 test participants showed worse results in their auditory discrimination performance upon field exposure as compared with control conditions ($p=0.0105$).

Curcio et al. [Curcio, et al. 2004] investigated the time-course of electromagnetic field (EMF)-induced effects on human cognitive and behavioral performance and on tympanic temperature. Subjects were randomly assigned to two groups, exposed to a GSM-900 signal before the testing session, or to the same signal during the data collecting session (maximum local SAR of 0.5 W/kg). Using a double-blind paradigm, subjects were tested on four performance tasks: an acoustic simple reaction time task, a visual search task, an arithmetic descending subtraction task and an acoustic choice reaction time task. Moreover, tympanic temperature was collected five times during each session. Results indicated an improvement of both simple and choice reaction times and an increase of local temperature on the exposed region under the active exposure. No effects were seen on the visual search task or the arithmetic descending subtraction task. There was a clear time-course of the reaction time and temperature data, indicating that performance and physiological measures need a minimum of 25 min of EMF exposure to show appreciable changes.

The so called TNO study from the Netherlands described in the previous chapter on symptoms also examined the effects of RF signals from mobile phone base stations on cognitive functions[Zwamborn, et al. 2003]. Cognitive functions were measured during exposure. In the cognitive function tests (reaction time, memory comparison, dual-tasking, visual selective and filtering irrelevant information), statistically significant differences were seen more often than should occur by chance (due to statistical noise), but there was no consistent pattern of results across the three signals, the different cognitive tasks or the two study groups. Independent replication of these findings would be useful.

In summary, recent results on RF exposure and cognitive functions have not clarified the picture. Changes in cognitive functions have been reported but, as stated by AGNIR (2003), the results are inconsistent and no single clear effect on cognitive function can be identified.

ELF fields

Possible effects of low frequency fields on human cognition and performance were reviewed in the recent ICNIRP (2003) report, and concluded as follows: *"In summary, some changes of magnetic fields on reaction time and accuracy have been reported but the effects were not consistent between studies. For memory and vigilance, there are essentially no reported effects. Further studies are required to clarify these issues* [possible effects on reaction time and accuracy]. *In addition, the nature of these effects makes it difficult at present to assign them any importance with regard to health impairment"*. Similar conclusions were reached in a recent review [Crasson 2003]: *"The psychophysiological and cognitive studies indicate that we cannot exclude the possibility of 50-60 Hz weak magnetic field exposure on human cognitive processes. The observed effects, however, are small…Effects are inconsistent, subtle, transitory and specific to some aspects of cognitive functioning, without a clear dose-response relationship, and difficult to reproduce."*

After the completion of the 2003 reviews by ICNIRP and Crasson, Kurokawa et al. [Kurokawa, et al. 2003] examined acute effects of 50-Hz magnetic fields on cognitive performance in humans. Twenty young subjects were exposed to circularly polarized 20-μT fields for 55 min, during which they performed four cognitive performance tests for evaluation of simple reaction time, time and accuracy of choice reaction, time perception, and figure perception. None of the subjects detected the existence of the field, and no effects on performance in the tests were observed.

The new results on ELF fields have not provided any such information that would alter the conclusions of the previous reviews (the earlier positive studies generally used stronger fields than Kurokawa et al.).

EEG and sleep

EEG and sleep studies are here considered together, as EEG monitoring is being used as a major tool in sleep research and several of the results are related to EEG during sleep.

A few research and review papers mainly dealing with RF exposure have recently been published that are reviewed below:

In Switzerland, Huber et al. had shown effects on waking regional cerebral blood flow (rCBF) and on waking and sleep electroencephalogram (EEG) in humans [Huber, et al. 2002]. Exposure to GSM-900 was on one side of the head during 30 min and the spatial peak SAR in the head was 1 W/kg. The authors used PET[4] to monitor rCBF following the exposure. They also recorded the quality of sleep during night-time sleep. The rCBF increased on the side of the head exposed and the EEG power was altered. However, continuous signals did not elicit this effect.

[4] positon emission tomography

More recently, the same group exposed the volunteers either during sleep or during the waking period preceding sleep [Huber, et al. 2003]. In the first experiment, subjects were exposed intermittently during an 8-hour night-time sleep period and, in the second experiment, on one side of the head for 30 min before a 3-hour daytime sleep period. Compared to the control condition with sham exposure, the spectral power of the non-REM[5] sleep EEG was initially increased in the 9-14 Hz range in both experiments. Unilateral exposure during waking induced a similar effect in both hemispheres of the brain. Some characteristics of the sleep pattern were altered. The authors interpret the effects as originating from a structure below the cortex such as the thalamus which was similarly exposed at around 0.1 W/kg.

These two studies have been carefully planned and performed and have yielded some interesting data. The amplitude of the effects remains small and of unknown consequences for health. However, further investigations will help ascertain the existence of the effects and their possible mechanism.

In Finland, Krause and co-workers recently published the results of a replication of their own work [Krause, et al. 2004]. The effects of GSM-900 exposure on the event-related desynchronization/synchronization (ERD/ERS) of some of the EEG frequency bands were studied in 24 normal subjects performing an auditory memory task. In this double-blind study, all subjects performed the memory task both with and without exposure in a counterbalanced order. The authors were not able to replicate the findings from their earlier study. Also, the effect of exposure on the number of incorrect answers in the memory task was inconsistent. They concluded that GSM-900 effects on the EEG and on the performance of memory tasks is variable and not easily replicable for unknown reasons.

In the three human studies described below, various approaches were used for exposure and EEG monitoring but several shortcomings, in particular in terms of dosimetry, make it difficult to agree with the authors' conclusions about the existence and relevance of effects of exposure on EEG:

- In the Australian study of D'Costa and co-workers, EEG recordings from 10 awake subjects were taken during exposure to a GSM phone positioned behind the head, the antenna pointing toward the head [no estimation of SAR was given for this unusual exposure situation] [D'Costa, et al. 2003]. Two experimental trials were conducted. In the first trial, the GSM mobile phone had its speaker disabled and configured to transmit at full-radiated power. In the second trial, the mobile phone was in active standby mode. For each trial, subjects were exposed under single-blind conditions in 5-min intervals to a randomized, interrupted sequence of 5 active and 5 sham exposures. The average EEG band power in active exposure recordings was compared to corresponding sham recordings. The EEG alpha (8-13 Hz) and beta (13-32 Hz) bands showed differences when the full-power mode was used.
- Kramarenko and Tan, in Ukrainia, recorded EEG changes during exposure of volunteers to a GSM phone on stand-by [Kramarenko and Tan 2003]. They claim to have suppressed the interference caused by emission from the phone and observed changes in EEG patterns: after 20-40 s, a slow-wave delta activity (2.5-6.0 Hz) appeared in areas on the side of the phone. After turning off the mobile phone, slow-wave activity progressively disappeared. They observed similar changes in children,

[5] REM: rapid eye movement i.e. "dream phase" of sleep

but the slow-waves with higher amplitude appeared earlier in children. According to the authors, these results suggested that cellular phones may induce abnormal slow waves in EEG of awake persons. However, it is most surprising that they were able to record slow-waves in awake volunteers and to transmit the signal by telemetry. Moreover, the dosimetry was not well described. Overall, this study does not bring new evidence on EEG effects of exposure.

- In the Estonian study of Hinrikus and co-workers, 20 healthy volunteers were exposed to 450-MHz microwaves with 7-Hz on-off modulation [Hinrikus, et al. 2004]. The field power density at the scalp was very low (0.16 mW/cm^2, at the scalp 10 cm away from the antenna, i.e. 9.5 mW/kg in the brain). Microwave stimulation caused changes in EEG in the frontal region. Changes varied strongly from subject to subject but overall, alterations of EEG were not statistically significant.

Few results have been reported on animals in recent years. Marino and co-workers studied the potential nonlinear changes in brain electrical activity due to cell phone exposure in rabbits [Marino, et al. 2003]. When the animals were exposed to the radiation from a mobile telephone (800 MHz, 0.6 W maximum emitted power), under conditions that simulated normal human use, the EEG was affected in nine of the ten animals studied. The effect occurred 100 ms after the onset of exposure and lasted approximately 300 ms. Absorption of the radiation by the EEG electrodes could not account for the observed effect. No effect was seen when exposure of the brain was minimized by moving the antenna from the head to the chest. The authors concluded that exposure to a standard mobile telephone can alter brain function. However, great caution again must be taken to interpret these data obtained during exposure on a short time scale. Extrapolation to human health is questionable even if the effect were real.

Three reviews have been published recently:

- Cook and co-workers dealt mainly with ELF exposure (and ELF-modulated RF) [Cook, et al. 2002]. The conclusion for ELF was that "The investigation of weak (below 500 μT), extremely low frequency (ELF, 0-300 Hz) magnetic field (MF) exposure upon human cognition and electrophysiology has yielded incomplete and contradictory evidence that MFs interact with human biology."

- Hamblin and Wood reviewed 14 papers on EEG and sleep related to GSM exposure [Hamblin and Wood 2002]. They concluded that, in general, outcomes have been inconsistent and comparison between individual studies was difficult. However, enhanced EEG alpha-band power has been noted in several of the studies, a phenomenon also observed in some animal studies. Since this alteration had been found in some ELF work, the authors suggested that the effect could be caused by exposure to the ELF magnetic field produced by the phone battery. Effects have been reported to occur both during exposure and up to 1 hour or so after cessation of exposure. It is however difficult to agree with the authors about the possible role of the magnetic field produced by the phone in eliciting the effects as there are no well-established effects of ELF magnetic fields on EEG (see above) and as the magnetic field is produced only very close to the phone, which in some of the investigations on EEG was not even in contact with the head.

- The review by D'Andrea and co-workers is part of an ICES series of "white papers" on microwaves and health [D'Andrea, et al. 2003]. The authors concluded that effects reported on sleep EEG are more likely to involve non REM alpha waves,

compared to other bands. Serious deficiencies in EEG human studies using EMF exposure included poor dosimetry making it difficult to compare results among experiments and laboratories. The authors concluded that "*no conclusions can be drawn from the present EMF–EEG research. If EMF–EEG research continues, the simplest of paradigms, and traceable dosimetry must be considered. The relation of the antenna to the brain must be defined in stereotaxic coordinates and the SAR fully mapped in the brain experimentally and numerically*."

Conclusion on EEG and sleep

Recent investigations on humans and animals have not added clear evidence of alteration of EEG and/or sleep. In any case, the relevance of minor alterations on EEG and sleep on health is not significant. Further investigations on sleep are ongoing and may bring some new information on these subtle effects.

Memory

From the AGNIR report [NRPB 2003]*: "The evidence from several laboratories indicates that changes may be induced in cholinergic activity in the brain following intense exposure. Such changes might predict effects on spatial learning and memory, but the evidence for this is equivocal: two studies from one laboratory have reported deficits in performance of spatial memory tasks using pulsed microwaves. But field-dependent changes were not confirmed in two independent studies using GSM signals. In addition. significant deficits on the performance of a related task were seen only when exposure increased body temperature by 2°C. Nevertheless, few tasks and exposure conditions have been examined and the available results do not rule out the possibility that microwaves may engender subtle cognitive or behavioural changes in immature or adult animals."*

Animal studies

Beyond the few studies that have concerned human memory, most of the research activity has been devoted to the replication and conformation of the results of the Lai group obtained on rats exposed whole-body to pulsed RF fields at 2.45 GHz [Lai, et al. 1994; Wang and Lai 2000]. See also the next chapter on results from some recent studies within the European Union 5th research program.

Both the groups of Cobb and Cassel who did replication studies using the exposure system of Lai found no evidence of impairment of memory in rats exposed at 2.45 GHz [Cassel, et al. 2004; Cobb, et al. 2004]. In parallel, the groups of Edeline and Sienkiewicz found no effect on spatial memory in rodents exposed using GSM signals [Dubreuil, et al. 2002; Dubreuil, et al. 2003; Sienkiewicz, et al. 2000].

The conclusion is thus today that there is no evidence of an effect of exposure to RF on memory of rodents. Since it was not clear what was the behavioural parameter tested in the Lai experiments (spatial memory, visual memory, performance, anxiety, etc.), further studies have recently been performed by the Cassel group on anxiety using an elevated plus maze and no effects were seen [Cosquer, et al. 2004].

However, Lai has recently published data on the effect of magnetic field noise that suppresses the effect of microwaves on rodent memory [Lai 2004]. It is thus surprising that the effect seems to be present in his laboratory and not in others and even more that "magnetic noise" suppresses the effect, as there is no solid evidence today that such ELF fields can remove bioeffects of ELF fields.

Human studies

Edelstyn and Oldershaw found that human volunteers exposed to mobile phones showed improvement in the performance of three cognitive function tests: (i) immediate verbal memory capacity, (ii) immediate visual spatial working memory capacity, and (iii) sustained attention [Edelstyn and Oldershaw 2002].

Two recent RF human cognitive studies have been performed [Haarala, et al. 2003; Krause, et al. 2004]; both were double-blind studies that failed to replicate some earlier findings [Koivisto, et al. 2000].

In conclusion, while there is no evidence that memory of rodents is affected by exposure to RF fields, the data are still inconclusive in humans, even if effects are of small amplitude and do not seem to be detrimental.

Results from some recent studies within the European Union 5th research program

National results from the INTERPHONE study

In the beginning of this year results were reported from a Danish case-control study of acoustic neuroma and mobile phone use [Christensen, et al. 2004], that is part of the INTERPHONE study. Information about mobile phone use was collected through personal interviews with 106 cases and 112 randomly selected controls matched on age and sex. Persons who were regular mobile phone users did not have an increased risk of acoustic neuroma (relative risk=0.9; 95% CI 0.5-1.6). The relative risk did not increase regardless of duration of use, amount of use, or time since first regular use. The number of long-term users was, however, small; only two acoustic neuroma cases and 15 controls had started to use a mobile phone more than ten years prior to diagnosis (RR=0.2; 95% CI 0.04-1.1).

During the fall, results from the Swedish part of the INTERPHONE study were reported [Lönn 2004; Lönn, et al. 2004]. The analyses were based on 644 brain tumor cases, 148 acoustic neuroma cases, and 674 randomly selected controls stratified on age, sex, and geographic region (604 controls in the acoustic neuroma analyses). Mobile phone use that started less than 10 years prior to diagnosis was not associated with an increased risk of any of the studied tumor types, whereas mobile phone use that started at least 10 years prior to diagnosis was associated with an increased risk of acoustic neuroma (RR=1.9; 95% CI 0.9-4.1, based on 14 exposed cases), which was confined to the side of the head where the phone was usually held (RR=3.9; 95% CI 1.6-9.5). For brain tumors, no indications of increased risks were found, regardless of duration of mobile phone use, or if analyses were restricted to the tumor location where the exposure is highest.

The results for short term mobile phone use in these two studies are consistent with the majority of previous reports [Auvinen, et al. 2002; Dreyer, et al. 1999; Inskip, et al. 2001; Johansen, et al. 2001; Muscat, et al. 2002; Muscat, et al. 2000], although the numbers of long term users in previous studies have been too small. The only previous studies that have consistently observed increased risks found risk elevations after a short duration of mobile phone use, and for several different types of tumors [Hardell, et al. 2002; Hardell, et al. 2001], which is not consistent with the studies described above.

Combined Effects of Electromagnetic Fields with Environmental Carcinogens (CEMFEC)

In the CEMFEC project, coordinated by the University of Kuopio and funded by the 5th Framework Research Program of the European Union, cocarcinogenic effects of low-level GSM-type radiofrequency (900 MHz) radiation were evaluated in a 2-year animal study conducted in compliance with the OECD Principles of Good Laboratory Practice (GLP). The known carcinogen used to induce cancer was the drinking water mutagen (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone, MX), which is known to act as a multi-site carcinogen in Wistar rats. Female Wistar rats (72 animals/group) were exposed to RF fields at two exposure levels (Specific Absorption Rates of 0.3 W/kg and 0.9 W/kg) for 2 h per day on 5 days per week. At the end of the 2-year study, tissue samples were collected for histopathology.

After 3, 6 months and 2 years of exposure, blood samples were collected (20 animals/group) for genotoxicological assays. Brain and liver tissue samples were taken for the same purpose at the end of the study. The comet assay was used to detect DNA damage and the micronucleus test to detect chromosomal aberrations (structural chromosome damage) and genome mutations (aneuploïdy induction).

Also *in vitro* studies using two cell lines were conducted to investigate whether RF electromagnetic fields affect selected cellular events that have been proposed as mechanisms for non-genotoxic carcinogenesis or cocarcinogenesis. In addition to MX, another environmental chemical (the fungicide Vinclozolin, or 3-(3,5-dichlorophenyl)-5-methyl-5-vinyloxazolidine-2,4-dione) was tested for combined effects with RF radiation. The mammalian cell lines NIH3T3 and L929 were used. Several endpoints were evaluated, including oxidative stress, cell proliferation, cell cycle analysis, apoptosis, mitochondrial membrane potential modifications and gene expression (proto-oncogens: c-fos, c-jun and c-myc). The SAR levels were similar to those of the animal study (0.3 W/kg and 1.0 W/kg).

The results of the animal study confirmed the carcinogenic effect of MX, but the RF exposures did not affect statistically significantly the incidence of any tumour type.

RF exposure did not induce genotoxic effects in blood, liver or brain. There were indications of a slightly decreased genotoxic response in the RF-exposed animals in blood cells collected at 3 and 6 months. These differences lost statistical significance after 24 months of exposure. RF exposure did not affect the level of DNA damage in liver or brain, either.

The *in vitro* experiments did not show any consistent effects on oxidative stress, apoptosis, mitochondrial membrane potentials or expression of selected oncogenes. However, both RF alone and in combination with the chemical exposures suppressed cell growth. This effect was dependent on exposure time (seen only after 24 h of exposure).

Based on the results of the animal study, cocarcinogenic effects of RF fields are not likely in this experimental model and at the exposure levels chosen. This conclusion is supported by the fact that no enhancement of *in vivo* genotoxic effects were found, and by the fact that *in vitro* studies did not show enhancement of the effects of the two chemicals or any effects characteristic to non-genotoxic carcinogenesis. In fact, according to current understanding of carcinogenesis, both the suggestive “protective” effect of the RF exposures against DNA damage and the slightly decreased proliferation in RF-exposed cells (if confirmed in further studies) should reduce rather than increase cancer risk.

The fact that SAR values higher than 1 W/kg were not used may be considered a limitation of the project. However, use of higher values might have caused thermal effects and thus problems with the interpretation of the results.

In summary, the results of the CEMFEC study should be interpreted together with other completed and ongoing studies using different experimental models and varying exposure levels.

Perform B: *In-vitro* and *in-vivo* Replication Studies Related to Mobile Telephones and Base Stations

The Perform B research programme lasted two and a half years and just ended. It was entitled “*In-vitro* and *in-vivo* Replication Studies Related to Mobile Telephones and Base

Stations." The PIOM laboratory in Bordeaux, France was the co-ordinator of the programme.

Its objective was to provide key research results which, when combined with current and past studies on the effects of radiofrequency radiation (RFR) on living systems, would contribute to an adequate database for health risk evaluation by public health authorities. It addressed specifically *in vitro* and *in vivo* replication studies recommended by the WHO agenda of 1999.

Two different biology laboratories were involved in each of the three proposed studies. The main emphasis was thus on replication rather than on mechanistic investigations.

Several exposure systems were designed or adapted: *in-vitro* systems (waveguides at 900 and 1800 MHz; TEM cells, wire-patch cell and STUK resonator chamber), *in-vivo* (Mini Wheel, Mainly-Head and Circular Waveguide Setups). These systems were developed to provide technical quality control during the entire period of exposure. A thorough dosimetry was implemented including an analysis of possible artefacts, the continuous monitoring of exposure and environmental parameters and blinded exposure protocols.

The three investigations have dealt with (i) genotoxicity, (ii) ODC activity in cells, and (iii) memory of rodents.

Using CW RF exposure at 935.2 MHz, Maes et al. had shown a weak increase in sister chromatid exchange in human lymphocytes consecutively treated with the genotoxic chemical mitomycin C (Maes et al., 1997). However, the Maes group was unable to replicate the data and thus a physical instead of chemical genotoxic agent was used in combination with RFR. Several standard *in vitro* tests for chromosomal and DNA damage in human lymphocytes were used. It was examined whether in these assays a 935 MHz GSM signal delivering SARs of 1 and 2 W/kg and a signal at 1800 MHz and 1 W/kg are genotoxic per se or can influence the genotoxicity of X-rays. Within the experiment parameters of the present study, in all instances no positive effect from the RFR signal was observed.

Ornithine decarboxylase, ODC, is a "marker enzyme" for cellular proliferation. The Litovitz research group has reported a temporary increase in ODC activity in L929 fibroblasts after exposure to RFR emitted from mobile phones (Penafiel et al., 1997). Only modulated RFR exhibited an effect on the ODC enzyme, compared to continuous wave signals (CW). All results of the Perform B programme did not support the previously reported effect of RFR on the activity of the ODC enzyme. The replication of the former work of the group of Litovitz, using 835 MHz/DAMPS and CW signals and murine L929 fibroblasts was extended to various RFR signals and to various cell types, including primary and live cells. Reminding that at least a ten-fold increase in ODC activity is necessary to induce deleterious effect on cellular functioning, the results give also no support for the possibility of neoplastic transformation via an effect on ODC activity.

There was limited animal evidence from the Lai group [Lai, et al. 1994] to suggest that pulse-modulated microwave radiation can transiently decrease radial arm maze performance in rodents (see also the previous chapter on memory). This is indicative of an effect on spatial working memory, a function associated in both rodents and humans with a part of the brain called the hippocampus. However, the results of the Perform B groups do not suggest that exposure to either pulsed 2.45 GHz fields or GSM-900 signals cause adverse effects on spatial working memory in either rats or mice. Moreover, exposure to pulsed 2.45 GHz fields affects levels of behavioural anxiety in rats, or significantly affects the

permeability of the BBB *in vivo*. In addition, similar negative results were obtained in mice whether they were exposed over the whole body or exposure was confined mainly to the head region. In particular, these experiments failed to confirm the results of studies performed by Lai and co-workers suggesting that exposure to RF fields induce large changes in maze behaviour in rodents.

While these studies do not rule out possible more subtle effects on other aspects of cognition in animals, they strongly indicate that generalised deficits in behaviour are unlikely to occur.

REFLEX: Risk Evaluation of Potential Environmental Hazards from Low Energy Electromagnetic Field (EMF) Exposure Using Sensitive in vitro Methods

The co-ordination of this European programme was done by the Verum Foundation in Munich. Twelve laboratories were involved in this highly structured multicentric study on ELF and RF field effects in vitro.

ELF magnetic fields
Genotoxic effects were studied on primary cell cultures of human fibroblasts and on different cell lines. DNA strand breaks were observed in human fibroblasts at a significant level at 35 μT [Ivancsits, et al. 2003a; Ivancsits, et al. 2003b; Ivancsits, et al. 2002]. The genotoxic effect was only observed when cells were exposed to intermittent fields and not to continuous exposure. The effect differed among the other types of cells examined. Confirmation studies in human fibroblasts in two other Reflex laboratories were carried out, with opposite results (one confirmed while the other did not). Chromosomal aberrations were also observed after exposure of human fibroblasts. Other observations were made in different laboratories: (i) ELF-EMF at around 2 mT upregulated the expression of early genes, such as p21, c-jun and egr-1, in p53-deficient mouse embryonic stem cells, but not in healthy wild-type cells [Czyz, et al. 2004b], (ii) ELF-EMF at 0.1 mT increased the proliferation rate of neuroblastoma cells, and (iii) ELF-EMF at 0.8 mT increased the differentiation of mouse stem cells into cardiomyocytes [Ventura, et al. 2004]. However, no effects were found on DNA synthesis, cell cycle, cell differentiation, cell proliferation and apoptosis in different cell types.

Thus, the few positive data on DNA damage originating from the Reflex programme appear to be in contradiction with results published in the literature. However, effects of intermittent ELF exposure have not yet been sufficiently investigated and therefore one must be careful in concluding about these data.

RF fields
Some genotoxic effects were reported in fibroblasts, granulosa cells and HL60 cells. Cells responded to RF exposure between 0.3 and 2 W/kg with a significant increase in single and double strand DNA breaks and in micronuclei frequency (not published). Chromosomal aberrations in fibroblasts were also observed after exposure. Downregulation of the expression of neuronal genes in neuronal precursor cells and upregulation of the expression of early genes in p53-deficient embryonic stem cells were observed at 1.5 W/kg, but not in wild-type cells [Czyz, et al. 2004a]. Proteomic analyses on human endothelial cell lines showed that exposure altered the expression and phosphorylation of numerous, yet largely unidentified proteins [Leszczynski, et al. 2002; Leszczynski, et al. 2004; Nylund

and Leszczynski 2004]. There was no evidence of effects on processes such as cell proliferation, apoptosis or immune cell functions [Capri, et al. 2004].

It is highly surprising that an effect of RF exposure could be present in a narrow range of SAR levels. One must thus await the publication in a scientific journal and replication of the positive data on DNA fragmentation which contradict all recent findings: a great majority of the published reports suggests that exposure of mammalian cells and animals does not result in increased DNA strand breaks, chromosomal aberrations, micronuclei and gene mutations (see Perform B above).

In conclusion, some of the positive data from the Reflex programme, when published, will warrant replication. However, research *in vivo* looking for effects possibly related to findings of the Reflex programme is premature, if not inappropriate.

Sensitivity of children to EMF

Introduction

Children in both industrialized and developing countries are exposed to a large variety of chemical, physical and biological environmental exposures. Real or perceived increases in the incidence of certain childhood diseases, such as asthma, leukemia and brain cancer, and some behavioral and learning disabilities are being linked to environmental factors. Environmental exposures can be particularly harmful to children because of their special vulnerability during periods of development, and also because of the type and magnitude of exposure and the potential irreversibility of deleterious health effects. With rapid advances in technology resulting in larger numbers of sources exposing people around the world to higher levels of electromagnetic fields (EMF) over much of the electromagnetic spectrum, questions have been raised as to whether EMF might have particular effects on children.

With the rapid advances in EMF technologies and communications that are being used by children at earlier and earlier ages, thorough discussion is becoming urgent. To evaluate the available information relevant to children's sensitivity to both ELF- and RF-EMF and to identify research needs, the World Health Organization (WHO) held an expert workshop in Istanbul, Turkey in June 2004. This part of our report is based on discussions and recommendations from that workshop.

Development of children

Embryos, infants, children and adolescents undergo different types of development. Development throughout the prenatal period is characterized by a highly ordered sequence of cell proliferation and differentiation, migration and programmed cell death (apoptosis). It is roughly divided into three periods: the preimplantation period, extending from fertilization to the settling of the embryo into the uterine wall; a period of organogenesis, characterized by the formation of the main body structures; and the fetal period, during which growth of the structures already formed takes place. The developing central nervous system seems to be particularly vulnerable because of the limited number and restricted physical location of the cohorts of proliferating cells from which it arises, and the precision required for building the complex neuronal architecture essential to proper brain function [Edwards, et al. 2003; Kimler 1998; Rodier 2004]. Major human tissue and organ development ends with the completion of sexual development at the end of the second or the beginning of the third decade of life. Development of the CNS continues through childhood and adolescence, largely through increased myelination and changes in synaptogenesis [Rodier 2004].

During the embryonic and fetal stages of development, exposure to environmental toxicants can result in death, congenital malformations, fetal or organ growth retardation, mental retardation, microcephaly, neurobehavioural effects, prematurity and stillbirth. During the postnatal stages of infant, child and adolescent development, exposure to toxic agents can result in total-organism growth retardation or selective tissue and organ retardation, cancer, interference with fertility and endocrine function, alterations in sexual maturation, interference with development of the immune system and alterations to neu-

rological development. Of particular relevance to EMF exposure are childhood leukaemia and brain cancer and cognitive development.

Several aspects of exposure and susceptibility warrant a focus on children. In some exposure scenarios children may receive higher doses than adults owing to higher intake and accumulation or to differences in behaviour. Greater susceptibility to some toxicants and physical agents has been demonstrated in children, and although the mechanism for this increased susceptibility is not well understood, it is likely to involve greater cell division in growing and developing tissues. However, the actual increase in sensitivity is frequently contested, and there are even some examples of increased resistance. In addition, a longer expected lifetime, with a consequently increased chance of repeated exposure and accumulated damage, can also lead to higher risk, particularly for cancer. Some effects may not be clinically evident until long after exposure to a toxic agent

Dosimetry for children

Numerous differences in the anatomy and physiology of children and adults are of particular consequence to dosimetry modelling for ELF and RF exposures. These parameters include differences in body shape and bone marrow distribution for ELF exposures; head size, skull thickness and ear elasticity for RF exposures; and dielectric properties for both.

In general, for ELF, adults exposed to low frequency electric or magnetic fields have higher internal electric field strengths and current densities than children because of size and shape differences. However, the distributions are different, and some tissues have higher current densities in children for the same external field. Furthermore, children have significantly higher internal field strengths and current densities from contact currents than do adults [Dawson, et al. 2001].

Modelling of SARs based on uniform or even nonuniform downscaling are inaccurate. To improve accuracy, MRI models, which take into account age-specific differences as well as variability between children, should be used. Despite large differences in the size, shape, and tissue distribution of heads, the SAR values and exposure variations for the child models are similar to those for adults, although somewhat higher. In addition, the relative depth of penetration is larger for children, a logical consequence of the smaller head diameter. Better modeling of the thickness of the compressed ears of children is needed. While some preliminary modeling indicated low exposure to fetuses, better models are being developed.

Dielectric studies encompassing several tissue types, including brain, obtained from newborn to fully grown rats, mice and rabbits exposed to RF-EMF in the frequency ranges of 130 MHz–10 GHz and 300 kHz to 300 MHz report large, age-related variations in the permittivity and conductivity of brain tissue, and even larger variations for skin and skull tissue [Peyman and Gabriel 2003; Peyman, et al. 2001; Thurai, et al. 1984; Thurai, et al. 1985]. Using age-related dielectric data to calculate whole-body and tissue-specific SARs in a scaled rat model led to significant differences in whole-body SARs. In addition, variations in tissue dielectric properties affect localized SAR values owing to corresponding variations of localized electric field and boundary conditions between neighboring tissues.

Exposure of children to RF and ELF Fields

In evaluating the potential role of environmental exposures in the development of childhood diseases, it is important to consider not only the fact that childhood exposures can be different from exposures during adulthood, but also the fact that they can be highly age dependent. Exposures of interest during the preconception and gestation periods include residential and parental exposures to ELF and RF fields as well as mothers' use of mobile phones, especially with a hands-free device. Infants and toddlers are exposed mostly at home or at day-care facilities. Among preteens, exposure sources expand to include mobile phone use and sources at school. Finally, adolescents are exposed to a wider variety of sources, including increasing use of mobile phones. Here we focus on two major exposure scenarios: residential ELF and RF exposures and exposure from mobile phones.

Everyone is exposed to ELF electric and magnetic fields at home. High-voltage power lines are a major source of exposure for children who live near them; however, only small proportion of children live in close proximity to high-voltage lines, in Sweden, for example, that number is less than one percent. There is evidence that younger children use appliances less (and spend less time outside the home), so that their personal exposure is closer to, and correlates better with, the field in the home.

RF fields are produced by radio and TV broadcasts, mobile phone base stations, and other communications infrastructure. Broadcast radio frequencies have been present for decades, but exposure to mobile phone signals has risen from zero in just a few years. While mobile phones are the dominant source of radiofrequency exposure for adolescents, environmental exposure to radio waves may be of concern for very young children. Note however, that exposure from base stations is orders of magnitude lower than that from mobile phones. The prevalence of mobile phone ownership among children is rising sharply and involves younger and younger children. In addition to the base stations, other sources such as TV and radio towers and deck phones at home contribute to the environmental RF exposure. Good information on population exposure and relative contributions of various sources is lacking. We consider it important for SSI to develop such information, which has become more feasible with the development of personal dosimeters.

When they reach adulthood, today's children will likely experience a longer period of exposure to RF fields from mobile phone and will have a much higher cumulative exposure than today's adults. However, rapidly changing technology might modify exposure. Radio-frequency exposure to children may be estimated more easily, because the variety of exposure sources is smaller for children than for adults.

Health effects

The interaction of EMF with biological tissue may involve either electric or magnetic fields, both of which are known to produce effects at relatively high levels. At these levels, ELF fields act inducing currents in tissue, while RF fields produce heating. Mechanisms that could possibly lead to effects at low exposure levels remain speculative. The vast literature on in vivo and in vitro experiments of both ELF and RF fields using a variety of cell systems and species is not reviewed here. Rather, we focus on the mechanisms and experiments most relevant to the potential sensitivity of children.

Extremely Low-Frequency Fields

Most carcinogenesis bioassays begin when animals are sexually mature. A number of assays have been published showing the absence of initiating and promoting effects of ELF magnetic fields. Importantly, an animal model for B-cell acute lymphoblastic leukemia, the most common leukemia among children, was lacking until recently. The results of an ongoing study of animals exposed to a 50-Hz magnetic field (100 μT) or a 50-Hz field plus harmonics using this newly developed model should be reported shortly [Bernard 2004]. These authors have found no evidence of an increase in incidence of leukemia in the exposed rats but have failed to provide positive controls showing that this animal model can be modulated. A number of in vivo studies have examined the effects of ELF fields on the responsiveness of the whole immune system. These studies have been carried out using differential white blood cell counts or standard in vitro tests of the immunological function of cells taken from the peripheral blood or spleen of exposed animals. The general consensus is that there is only weak evidence that power-frequency exposure can affect - and especially inhibit - the various aspects of immune system functions, including those relevant to cancer.

The potential risks to children of exposure to ELF-EMF, estimated from residential proximity to power sources and from measured fields, have been investigated in relation to in utero and postnatal time periods and to paternal exposure. Since an association between residential extremely low frequency electric and magnetic fields and childhood cancer, including leukemia, was first suggested in a report published in 1979, dozens of increasingly sophisticated studies have examined this association. Subsequently, a number of comprehensive reviews, several meta-analyses and two pooled analyses have summarized results from numerous sources. The two pooled analyses are closely consistent with each other and have reported the strongest associations between EMF and childhood leukemia in the literature: a risk of about two for children exposed to magnetic fields greater than 0.3 - 0.4 μT compared with children exposed to fields less than 0.1 μT [Ahlbom, et al. 2000; Greenland, et al. 2000]. Based on these results, IARC [IARC 2002] classified ELF magnetic fields as "possibly carcinogenic to humans." While the results of the pooled analyses are not likely to be due to chance or to a known confounder, bias cannot be ruled out. The assessment of exposure to magnetic fields has improved over time, yet our ability to predict exposure remains severely limited - although it might be better for children than for adults [Forssén, et al. 2002]. An epidemiologically detectable risk of leukemia for children, but not for adults, might result from either better exposure assessment for children, or from greater susceptibility in children. Initially, it appeared that the EMF association was stronger with childhood brain tumors than with leukemia; however, several of the most recent studies have found no association [Kheifets 2001]. While no consistent associations have been observed for childhood CNS tumors, pooled analyses (proven so informative for childhood leukemia) of brain tumor studies have not been done.

Radiofrequency Fields

Only a few studies have included prenatal or newborn rodent exposure. Adey et al. [Adey, et al. 1999] have exposed rats to American mobile telephone signals in utero. No effects were found on spontaneous tumorigenicity in the central nervous system in the

offspring of exposed rats. Moreover, a trend for a decrease in the incidence of primary CNS tumors was shown for rats treated with a single dose of the neurocarcinogen ethylnitrosourea in utero. In other bioassays, animals were usually five or six weeks old and sexually mature (comparable to teenagers) at the start of a 2-year exposure period. In these bioassays, young animals were exposed for part of or the rest of their lives. Initiation as well as promotion was investigated. All of the studies have reported negative results in normal animals at SARs compatible with mobile telephony (e.g. [Anane, et al. 2003], while controversy still exists about the carcinogenic effects of RF radiation in a transgenic model [Repacholi, et al. 1997]. Major replications of this work should be completed soon. Gatta et al. [Gatta, et al. 2003] showed that immunological parameters were not altered in mice with whole-body exposure to RF fields at a SAR of 1 and 2 W/kg. Although cell differentiation plays a central role in the development of organisms, only sparse information is available on the effects of RF radiation on differentiation. One study reported that exposure to RF fields at 1.5 W/kg up-regulated the expression of neuronal genes in neuronal precursor cells in p53-deficient embryonic stem cells, but not in wild-type cells [Czyz, et al. 2004a].

Several ecological studies [Cooper, et al. 2001; Dolk, et al. 1997a; Dolk, et al. 1997b; Hocking, et al. 1996; Maskarinec, et al. 1994; McKenzie, et al. 1998; Michelozzi, et al. 2002] have examined cancer risk, including risk of childhood leukemia, among populations living in proximity to radio and television broadcast towers. Driven by a previously identified cluster, these analyses are based simply on distance from the source and often include an extremely small number of cases. Such studies have been uninformative.

Developmental Effects and Pregnancy Outcomes

Extremely Low Frequency

Several studies, including a few with large group sizes and exposure over several generations, have evaluated exposure to electric fields of up to 150 kV/m in several mammalian species. The results of these studies are rather consistent, and do not suggest adverse developmental effects [Juutilainen 2003]. Magnetic field exposure has been evaluated both in non-mammalian and mammalian models. Results from several independent research groups suggest that exposure to ELF magnetic fields at microtesla levels may disturb early development of bird embryos. However, replication attempts have been unsuccessful in some laboratories. Results from experiments with other non-mammalian experimental models (fish, sea urchins and insects) have also suggested subtle effects on developmental stability. In mammals, prenatal exposure to ELF magnetic fields does not result in strong adverse effects on development. Gross external, visceral or skeletal malformations are not increased by fields of up to 20 mT (at 50 Hz). The only finding that shows some consistency is an increase in minor skeleton alterations in several experiments, in both rats and mice. Skeletal variations are relatively common findings in teratological studies and are often considered biologically insignificant. Nevertheless, subtle effects of magnetic field exposure on skeletal development cannot be ruled out. Some effects of magnetic (or combined electric and magnetic) fields on postnatal development have been reported, but evaluation of the consistency of the findings is difficult owing to the varying methods and approaches used in different studies.

Numerous epidemiological studies of various pregnancy outcomes in relation to EMF are available in the scientific literature. They include studies investigating the use of video

display terminals (VDTs), electric blankets or heated waterbeds, as well as studies of parental occupational exposure. Most studies have found no effects, but these studies are limited in exposure assessment and lack the power to examine high exposure levels. Two studies that have included personal measurements of ELF-EMF exposure have reported effects on spontaneous abortion in relation to maximum measured magnetic fields [Lee, et al. 2002; Li, et al. 2002]. The possibility of exposure assessment bias in these studies has been discussed, and results need to be confirmed in additional studies before firm conclusions can be drawn.

Radiofrequency Fields

Numerous studies have evaluated developmental effects of RF fields on mammals, birds and other non-mammalian species [Heynick and Merritt 2003]. These studies have shown clearly that RF fields are teratogenic at exposure levels that are high enough to cause significant increases in temperature. There is no consistent evidence of effects at nonthermal exposure levels.

Several studies of occupational RF exposure, primarily to physiotherapists, have reported an increased risk of congenital malformations. However, no specific type of malformation has been consistently reported, and there is a potential for recall bias in these studies. Exposure to the fetus from a mobile phone kept in a pocket, handbag, or belt by the hip when a pregnant woman is using hands-free equipment has been mentioned. So far, no studies are available on pregnancy outcomes related to mobile telephony.

Behavioural and Cognitive Effects in Children

Effects on brain function that lead to detrimental effects on cognition and behavior can be due to the high sensitivity of the developing and maturing nervous system to particular physical and chemical agents. Very few laboratory studies of the effects of RF fields and no studies of the effects of ELF fields on children appear to have been performed. Extrapolation of acute effects is necessary, using results from studies of adult volunteers and studies of both immature and adult animals. Although such extrapolation may provide some qualitative information regarding potential outcomes in children, it may not provide reliable estimates of risk.

Extremely Low-Frequency Fields

The results of acute exposure to magnetic fields on simple and choice reaction time in adult volunteers do not suggest any field-dependent effects, although modest changes in speed and accuracy during task performance have been reported. These data also suggest that effects may depend on the difficulty of the task performed. A few studies have reported subtle field-dependent changes in other cognitive functions, including the performance of specific memory and attention tasks. Studies measuring the electrical activity of the brain have reported scattered field-dependent effects and hints of subtle trends, but no well-defined, field-dependent results.

Various animal models have been used to investigate possible field-induced effects on brain function, electrical activity and behavior. These effects include changes in neurotransmitter levels, electrical activity, and the performance of learned tasks. Overall, while a few field-dependent responses, such as changes in spatial memory, have been tenta-

tively identified, the fragmented nature of the observed responses does not suggest an obvious deleterious effect. The available evidence is thus suggestive of subtle effects, but is not conclusive.

Radiofrequency Fields

Several recent studies have examined the effects of RF fields associated with mobile phones on attention, memory and other cognitive functions. No consistent responses have been observed, and these studies provide only weak evidence that changes in cognitive performance occur following low-level exposure. A few recent experimental studies have investigated the effects of exposure from Global System for Mobile Communications (GSM) signals at 902 MHz on child cognition [Preece unpublished]. Finnish researchers have recently investigated the effects of mobile phones on brain activity, cognitive functions and subjective symptoms in 10-14 year old children. Peer-reviewed publications are not yet available but according to a preliminary report [Haarala and Krause 2003], some effects were seen on EEG of children performing an auditory memory task, while no effects were observed on cognitive functions or subjective symptoms). In the other study, mobile phone exposure did not affect cognitive performance as measured by response speed and accuracy. One observational study found a mild facilitating effect on attention, as measured in paper and pencil tests, in adolescent users of mobile phones, but this may reflect changes in motor skills rather than attention per se [Lee, et al. 2001]. Several studies have reported that RF fields may affect the electrical activity of the brain. However, no specific response has been identified, and other studies have not reported any changes. Some, but not all, studies suggest that RF fields may affect certain components of sleep.

The possible effects of RF fields in animals have been investigated using a variety of approaches, from measurement of specific gene expression and neurotransmitter activity to investigation of changes in learned behaviors and in the electrical activity of the brain. The majority of reported RF effects appear to be consistent with hyperthermia or thermoregulation, or with stresses associated with exposure. Some data suggest that spatial maze behavior of rats can be impaired by exposure to pulsed RF fields in the absence of whole-body heating, although more recent studies found no significant RF effects. In addition, two studies indicate that the learned behavioral responses of adult rats were not affected by prenatal or early postnatal exposure to low-level RF fields.

Other Outcomes

Nothing is known about potential adverse health effects later in life from EMF (ELF and RF) exposures during childhood. Associations between occupational ELF magnetic field exposure and amyotrophic lateral sclerosis (ALS) and Alzheimer's disease have been reported, although alternative explanations to the findings are being discussed. There are also controversial reports that exposure to mobile-phone frequency fields affects the permeability of the blood-brain barrier. Perhaps we need to ask whether EMF exposure in childhood can increase the risk of developing Alzheimer's disease, brain tumors, or other outcomes later in life, especially in light of extensive mobile phone use among teenagers.

Research gaps

Physical, chemical and therapeutic agents have the potential for affecting development, depending on the nature of the agent and the timing and magnitude of the exposure. For ELF magnetic fields there are indications that children might be more sensitive; however, we lack the understanding of how, or even if, these fields might be involved in leukemogenesis. Several analyses can help advance the current state of knowledge, particularly on the potential effect of ELF on children. These include update of the pooled analysis of childhood leukemia, pooled analysis of brain cancer studies, studies of large highly exposed and/or susceptible populations, evaluation of selection bias and other hypothesis such as contact current and melatonin. Meanwhile, given the current state of science and despite the lack of a known mechanism precautionary approach is warranted.

Even less is known about the potential sensitivity of children to RF fields. Widespread exposure to these fields is recent, and although much of the laboratory research has been reassuring, its focus has not been on children. Moreover, few epidemiologic studies of adequate quality have been completed and even fewer are of relevance to children. Given the paucity of data indicating a particular vulnerability of children to EMF, it may be tempting to conclude that children are not more susceptible than adults to RF exposure. However, the absence of an observed effect does not necessarily mean that exposure is harmless, especially if crucial studies focusing on children are yet to be done. In addition, many of the methods used have not been sensitive enough to detect subtle effects. In the absence of direct evidence for or against the potential susceptibility of children to EMF, one can extrapolate either from data on adults or from data on other chemical and physical agents. Extrapolation from data on adults is problematic. Because the period from embryonic life to adolescence is characterized by growth and development, deleterious effects can occur at lower levels be more severe, or lead to effects that do not occur in adults; on the other hand, children can be more resilient, owing to better recuperative capacities. Extrapolating from other exposures is also problematic: while it is clear that children are more vulnerable to many physical and chemical agents, many of their effects are very specific in terms of both the level and timing of exposure. Thus, there is an urgent need to design and implement studies that can provide direct and relevant information on the potential susceptibility of children to RF exposure. Owing to widespread use of mobile phones and relatively high exposures to the brain among children and adolescents, investigation of the potential effects of RF fields on cognition

See www.who.int/peh-emf/research/rf03/en for more details on a research agenda that identifies high-priority studies needed to fully assess the potential vulnerability of children to ELF and RF fields and outlines the rationale for these studies.

Limited scientific evidence on the carcinogenicity of electric and magnetic fields - is it enough for precautionary preventive action?

Evaluating the risk related to various agents with potential to increase cancer risk in humans is often controversial. Several national and international health agencies have established programs with the aim of identifying carcinogens.

In principle, it is an activity grounded in the scientific evaluation of the results of human epidemiological studies, long-term bioassays in experimental animals and other data relevant to an evaluation of carcinogenicity and its mechanisms. In this brief commentary, we

discuss the interpretation of the categories adopted in the IARC Monograph program to identify carcinogens.

The IARC Monographs are using the following descriptors:

Table 1. IARC Categories of evidence

Categories	Cancer hazard to human
Group 1	the agent or mixed exposure is carcinogenic to humans
Group 2 A	the agent or mixed exposure is probably carcinogenic to humans
Group 2 B	the agent or mixed exposure is possibly carcinogenic to humans
Group 3	the agent or mixed exposure is not classifiable as to its carcinogenicity
Group 4	the agent or mixed exposure is probably not carcinogenic to humans

Epidemiological data in humans

Assignments to Group 1, human carcinogens, are made exclusively on the basis of human data, the experimental data playing no role (see Table 2). However, there are a few notorious cases, where an agent has been classified into the group in the absence of sufficient evidence of carcinogenicity in humans. An example is TCDD. This was done based on convincing animal data and good understanding of the mechanistic principles of cancer causation in rodents. There was enough evidence in humans which indicated similar mechanisms and also operative in humans, making the probability that TCDD would lasso be carcinogenic to humans high.

Table 2. Overall default evaluation of carcinogenicity in the IARC Monographs

		Cancer in experimental animals		
		Sufficient	Limited	Inadequate
Cancer in humans	Sufficient	1 Carcinogenic	1 Carcingenic	1 Carcinogenic
	Limited	2A Probably carcinogenic	2B Possibly carcinogenic	2B Possibly carcinogenic
	Inadequate	2B Possibly carcinogenic	3 Not known	3 Not known

In making the assessment of causation in humans, epidemiologists ask whether a causal association is credible and whether chance, bias, or confounding factors can be excluded. The guidance from the set of "Hill criteria" is searched, including

Consistency of the observed association
Strength of the observed association
Specificity of the observed association
Temporal relationship of the observed association
Biological gradient (exposure-response relationship)
Biological plausibility
Coherence
Experimental evidence (from human populations)
Analogy

Experimental Animal Bioassay Data

The most common way of identifying potentially carcinogenic agents is long-term bioassays in experimental animals. Experimental carcinogenesis research is based on the assumption that agents, which can cause cancer in animals, will have similar effects in humans. Within the IARC Monographs program, the respective roles of human and experimental data in defining and/or predicting human risk have been amply and repeatedly debated. It has been agreed that carcinogenic risk to humans could be quantified on the basis of experimental animal data only with large uncertainties. However, experimental evidence has maintained its validity in demonstrating carcinogenicity of and agent and in serving as an alert that similar effects, might occur in humans. Accordingly, the IARC monographs have a policy statement in the preamble, which states that in the absence of adequate human data, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans [IARC 2002]. In doing so, IARC, anticipating what later became known as the 'precautionary principle', was trying to reconcile a scientifically accurate analysis of the data with an interpretation of the evidence of carcinogenicity provided by experimental data that is not only biologically plausible but is public health orientated and gives priority to primary prevention.

Evaluation of the data on mechanisms

Consideration of the mechanistic data has the potential of improving the analysis of causation between the observed effect and the given exposure. Elucidation of the mechanisms gives insight into the potential steps important in the process and prevention of carcinogenesis. There may be strong associations between exposure and disease, but if confounding factors are not examined thoroughly, the association may be spurious.

The IARC categories and need for cancer prevention

The IARC categories are considered to be "hazard" assessments, not risk assessments, which would include an attempt for quantitation of the potential risk. This risk depends on both the existence of hazard and exposure to that hazard. A cancer hazard exists when an agent has been categorized to Groups 1, 2A and 2B (see Table 1). It should be emphasized that the categorization of an agent with regard to its carcinogenicity remains a matter of scientific judgment, and agents or exposures can be classified to different categories in a way different from the strict interpretation of the default criteria. In Group 1 the hazard has been shown to produce a real risk in humans (as observed in epidemiological studies of exposed humans). In Group 2A there are clear indications of the cancer hazard,

and in Group 2B the hazard is considered to be high enough to consider, for practical purposes, preventive actions. The agents which cause cancer in animal models, but do not have any relevant human data, are categorized in Group 2B as 'possible human carcinogens'.

The category 2B is generally used for agents for which there is limited evidence of carcinogenicity in humans in the absence of sufficient evidence of carcinogenicity in experimental animals, or when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. The above mentioned public health statement in the IARC Monographs preamble that agents with 'sufficient evidence' in experimental animal models should be considered, for practical purposes and for the purpose of primary prevention, 'as if they presented a carcinogenic risk to humans' should logically also apply to all agents in this category 2B of 'possible human carcinogens'. The preventive approaches to be considered could include strategies to reduce exposures as much as technologically possible, strategies to search for alternative chemicals/agents etc.

Evaluation of carcinogenicity of electric and magnetic fields in the IARC Monographs

Exposure to electric and magnetic fields (EMF) emanating from utilization of electricity is widespread. The major concern has focused on the possibility that exposure to extremely low-frequency (ELF) electric and magnetic fields may result in increased risk of cancer. It is a widely held view that the current scientific evidence in support of an association between ELF magnetic fields and childhood leukemia is limited [IARC 2002]. The evaluation in the IARC monographs lead to overall evaluation of Group 2B, ELF magnetic fields being possibly carcinogenic to humans. Evidence for static electric and magnetic fields and ELF electric fields is not classifiable as to their carcinogenicity to humans (Group 3). As far as radiofrequency fields (RF) are concerned, the evaluation in the IARC Monographs has not yet been done, and it is planned to take place in 2006.

Developing Policy for Children

Given the paucity of data indicating a particular vulnerability of children to EMF, there is an urgent need to develop policies in the face of uncertainty and to design and implement studies that can provide direct and relevant information on the potential susceptibility of children.

Setting Guidelines

Guideline-setting bodies often recognize that children might be more susceptible to EMF than adults, that EMF dosimetry is different in children and that behavior, and thus exposure, might be different in children. The potential for these differences is incorporated in an additional reduction factor that is applied to exposure limits for the general population (as compared to limits for occupational exposure), rather than the development of specific limits for children.

The exposure guidelines developed by the International Commission on Non-ionizing Radiation Protection (ICNIRP) are intended to protect against adverse health effects that are scientifically established. In the case of electromagnetic fields, all established effects

are acute ones [ICNIRP 2002] with specific thresholds, in the sense that a minimum biologically effective quantity must be applied for an effect to occur. In this approach, the concept of *critical effect* is fundamental. The critical effect is the established adverse health effect that occurs at the lowest level of exposure. If a given effect were found to occur in children - or in any other particular group - at an exposure level lower than that required for an effect in the rest of the population, it would be assumed to be critical. Sources of uncertainty include possible differences between children and adults in the distribution of induced currents and in SARs (for low- and high-frequency fields, respectively). The reduction factor of 5 used for both ELF and RF exposures for the general population is likely to be adequate for the protection of children against established health effects.

Precautionary Approaches

The precautionary principle is an attempt to link the scientific community and the community of 'common' people in joint responsibility for decisions, a state where primary importance attaches to our right to be informed and our freedom of choice. Risk involved in electromagnetic fields may well be lower than in many other areas currently well accepted (such as risks of motor traffic), but public opinion bluntens the perception of certain risks, as in case of ultrafine particles from motor exhausts. Scientific evidence can make its contribution to societal decision making openly, to clarify the contours of uncertainty with the reservations typical of scientific rationality. For its part, the political decision making procedure must supply the tools and channels for democracy to find its voice.

While development of science-based guidelines for established effects is challenging, development of science-based precautionary approaches for uncertain effects is even more difficult, particularly when children may be affected. Many societies have a heightened level of concern for vulnerable populations, particularly children, because they may be unable to take actions to effectively manage their own risk. Furthermore, many societies believe that children and fetuses should be afforded an even higher level of protection because they represent the future of the society (WHO Precautionary Framework, 2004). Other factors, such as the potential number of productive years lost and the potential for higher and longer exposure, also come into consideration. Finally, widespread exposure can have large public health consequences even if its effects are small or subtle.

The draft WHO Precautionary Framework discusses several factors that argue for the adoption of greater, rather than lesser, protection for EMF exposure to children. Among these factors are the possibility that EMF might affect children; the dread with which some of the diseases in question, such as leukemia and brain cancer, are perceived; the involuntary nature of some of the exposure; the extensiveness of exposure; the rapid growth of some exposures; and the occurrence of some of the exposures to children close to guideline limits. Possible precautionary measures for EMF will vary from country to country, but should follow WHO Precautionary Framework recommendations as outlined in the case studies. In Sweden, such approaches have already been introduced for both ELF and RF fields.

The precautionary principle emerged as a decision rule for regulating environmentally hazardous activities in the Swedish Environmental Protection Act of 1969. This act which remains in effect today incorporates the statement that the mere risk of harm, if not remote, warrants protective measures or a ban on the activity that is possibly causing harm.

For low frequency fields, the Swedish Radiation Protection Authority recommended reducing exposures specifically without providing any recommendation regarding levels. In 1993 the Swedish government, acting upon the recommendation of the Swedish Electric Board [Villa and Ljung 1993], advocated prudent avoidance. This cautionary policy, defined as taking measures to reduce magnetic fields in newly built housing and electrical facilities without great inconvenience or cost, was formalized in 1996 in a guide for Swedish local officials [National Board of Occupational Safety and Health, et al. 1996]: "If measures generally reducing exposure can be taken at reasonable expense and with reasonable consequences in all other respects, an effort should be made to reduce fields radically deviating from what could be deemed normal in the environment concerned. Where new electrical installations and buildings are concerned, efforts should be made to design and position them in such a way that exposure is limited."

For RF, the joint statement of Scandinavian Radiation Protection last year adopted precaution (2004)

"The existing knowledge gaps and the prevailing scientific uncertainty justify a certain precautionary attitude regarding the use of handsets for mobile telephony. Due to the widespread use of mobile phones even a very small risk could have consequences for public health. Because of the lack of knowledge in certain fields of research the Nordic authorities find it is wise to use, for instance, a hands-free kit that reduces the exposure to the head significantly. This information should be addressed both to adults, young people and children. It is important that parents inform young people and children about how to reduce the exposure from mobile phones."

Discussion

It is clear from the presentations and discussions in this report that there are several important ongoing studies and that there are several unresolved issues. Most of the current focus is on RF rather than on ELF or other lower frequencies. The most likely explanation to this is that ELF research began earlier and has come further. At least for the epidemiologic studies it may be reasonable to compare the current RF epidemiology to ELF epidemiology about a decade ago. A major explanation to this is that knowledge about exposure distribution in the population and measurement technology has developed further and is now much better for ELF fields. However, exposure assessment was a major obstacle in earlier ELF epidemiology and it remains so in current RF epidemiology. A number of second generation RF studies are in the process of being planned or piloted. A major issue in this process is the exposure assessment.

To date, little is known about the levels of radiofrequency exposure in the general population from sources such as mobile phones being used by oneself or other people, mobile phone base stations, and radio and television transmitters. Measurements that have been performed have usually been made as a result of public concern about base station exposures or other specific sources, and have therefore been made at locations that could be assumed to have higher fields than would be the case if measurement locations were selected randomly. Furthermore, all measurements have been stationary, and there is today no knowledge about the level of exposure that an individual will have throughout the day. Some countries have set up networks monitoring the radiofrequency exposure at certain locations, but again, the locations chosen have been driven by the existence of base stations or other RF exposure sources, and do not reflect the RF exposure in the general population.

There is a need for information about the personal exposure to RF fields in the general population, to enhance the understanding of the relative importance of exposure from base stations close to the home, from radio and television transmitters, and from the use of mobile phones. There is now a personal meter available that can measure the RF fields over a longer time period, e.g. 24 hours, and that has the possibility to distinguish between different sources of RF exposure. Studies with personal RF exposure measurements of randomly selected samples of the general population are strongly encouraged.

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SSI report

STATENS STRÅLSKYDDSINSTITUT, SSI, är central tillsynsmyndighet på strålskyddsområdet. Myndighetens verksamhetsidé är att verka för ett gott strålskydd för människor och miljö nu och i framtiden.

SSI är ansvarig myndighet för det av riksdagen beslutade miljömålet *Säker strålmiljö*.

SSI sätter gränser för stråldoser till allmänheten och för dem som arbetar med strålning, utfärdar föreskrifter och kontrollerar att de efterlevs. Myndigheten inspekterar, informerar, utbildar och ger råd för att öka kunskaperna om strålning. SSI bedriver också egen forskning och stöder forskning vid universitet och högskolor.

SSI håller beredskap dygnet runt mot olyckor med strålning. En tidig varning om olyckor fås genom svenska och utländska mätstationer och genom internationella varnings- och informationssystem.

SSI medverkar i det internationella strålskyddssamarbetet och bidrar därigenom till förbättringar av strålskyddet i främst Baltikum och Ryssland.

Myndigheten har idag ca 110 anställda och är belägen i Stockholm.

THE SWEDISH RADIATION PROTECTION AUTHORITY, SSI, is the government reguatory authority for radiation protection. Its task is to secure good radiation protection for people and the environment both today and in the future.

The Swedish parliament has appointed SSI to be in charge of the implementation of its environmental quality objective *Säker strålmiljö* ("A Safe Radiation Environment").

SSI sets radiation dose limits for the public and for workers exposed to radiation and regulates many other matters dealing with radiation. Compliance with regulations is ensured through inspections.

SSI also provides information, education, advice, carries out its own research and administers external research projects.

SSI maintains an around-the-clock preparedness for radiation accidents. Early warning is provided by Swedish and foreign monitoring stations and by international alarm and information systems.

The Authority collaborates with many national and international radiation protection endeavours. It actively supports the on-going improvements of radiation protection in Estonia, Latvia, Lithuania, and Russia.

SSI has about 110 employees and is located in Stockholm.

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