Recent Research on EMF and Health Risks. Third annual report from SSI's Independent Expert Group on Electromagnetic Fields.

SSI's Independent Group on Electromagnetic Fields, 2005

Preface

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

The composition of the group during 2005 has been:

Prof. Anders Ahlbom, Karolinska Institutet and Stockholm Center for Public Health, Stockholm, Sweden (chairman);
Prof. Jukka Juutilainen, University of Kuopio, Kuopio, Finland;
Dr. Bernard Veyret, University of Bordeaux, Pessac, France and University La Sapienza, Rome, Italy;
Dr. Harri Vainio, Occupational Health Institute, Helsinki, Finland (formerly at IARC, Lyon, France);
Prof. Leeka Kheifets, UCLA, Los Angeles, USA (formerly at WHO, Geneva, Switzerland);
Prof. Anssi Auvinen, University of Tampere, Tampere, Finland;
Dr. Richard Saunders, Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards, Oxfordshire, UK

Prof. Maria Feychting, Karolinska Institutet, Stockholm, Sweden, has been appointed scientific secretary to the group.

Stockholm in December 2005
Anders Ahlbom
Chairman

Executive Summary

ELF

Recent biology

A German research group has published additional data that support their previous results suggesting enhanced development of chemically-induced mammary tumours in a specific substrain of rats exposed to ELF magnetic fields. Some recent studies, e.g. within the REFLEX programme, suggest genotoxic effects from exposure to relatively weak magnetic fields. However, results from other recent studies were negative. Previous evidence for carcinogenic and genotoxic effects of ELF magnetic fields is inadequate and mainly negative. The recent studies have not established effects that would change the previous conclusions.

Recent epidemiology

The recent childhood leukaemia study from the UK is very large and uses digitized exposure information, which requires no access to study participants' homes and thus minimizes potential for selection bias. However, the current publication uses distance between home at birth and power line as proxy for EMF exposure. The authors acknowledge that this is a poor marker for exposure and we await further results based on calculated magnetic fields which we hope will be more informative.

RF

Recent laboratory studies

Several recent animal and cell culture studies have evaluated possible genotoxic effects of RF electromagnetic fields. Two research groups reported increased DNA strand breaks and micronuclei. However, these results are weakened by methodological limitations, and other studies reported no effects, which is consistent with the majority of previous studies. On balance, the recent studies reviewed, including those from the REFLEX programme, do not provide sufficient evidence to conclude that RF fields are genotoxic.

Blood-Brain Barrier

Most of the recent results of studies aimed at replicating earlier positive work have been negative at low SAR levels. Further studies on the permeability of the blood-brain-barrier or on damaged (darkly-staining) neurons are ongoing and should give more information on the issue. On balance, the evidence that exposure to RF fields alters the blood-brain-barrier is weak.

Human laboratory studies

Recent work on cognitive functions in volunteers (including children) exposed to RF fields has been negative; however, methodological limitations prevents firm conclusions.
There have been reports of some positive findings on alterations of sleep.
The data obtained on alteration of cerebral blood flow following RF exposure are among the most interesting observations of biological effects even if they do not point clearly to health effects.
Following all of the recent publications on hearing and in particular those originating from the European Commission's GUARD programme, one could now conclude about the absence of effects of RF exposure due to cellular phones at GSM frequencies, on the main parameters of the auditory system.

Recent epidemiology

Two recent Interphone studies on brain tumours suggest that there is no risk increase either for short-term or long-term use, although long-term data are sparse. A joint international publication of some of the studies taking part in Interphone on acoustic neuroma showed no effect for short-term use and no overall effect for long-term use. However, the laterality analysis did show a risk increase for ten or more years of use. Some other Swedish data have also been presented but they are given less weight in the overall analysis.

On balance the currently available evidence suggests that for adult brain tumours there is no association with mobile phone use for at least up to, say, ten years of use. For longer latency the majority of the evidence also speaks against an association, but the data are still sparse. The same conclusion holds for short-term use and acoustic neuroma. However, for long-term use and acoustic neuroma there is a concern, and more information is required. Furthermore, studies of children are yet to be done, as well as studies on outcomes other than cancer.

WHO

Environmental Health Criteria document on Static Fields

Static magnetic fields are generated wherever DC currents are used; exposure to flux densities of up to several millitesla (mT) occur for example in electric trains. However, the largest static magnetic fields (0.2 – 3 T) likely to be experienced by members of the public occur during exposure for clinical diagnosis to the fields generated by magnetic resonance imaging (MRI) systems. Effects caused by the large electrical fields generated around the heart are likely to limit patient exposure to MRI at very high field strengths. Other acute effects, such as vertigo and nausea, are reported to occur in workers during movement within and around MRI devices. However, with regard to the possible long-term effects of exposure to such high fields, there are no good epidemiological or long-term experimental studies. National authorities should implement programmes that protect both the public and workers from the untoward effects of such fields, and should conduct further research on the possible health effects of exposure.

Workshop on childhood sensitivity

There are biological and dosimetric differences between children and adults, some of which persist into adolescence, but as little research has specifically addressed potential vulnerability and health effects in children and there is no good evidence one way or another whether children are more susceptible to RF fields than adults. At power frequencies, a consistently increased risk of leukaemia is seen in children but not in adults.

Workshop on base stations

The workshop participants concluded that the likelihood of health effects from base station or other transmitter exposure is low. This was based on considerations of the very weak exposure from base stations, the lack of a known mechanism that could explain any effects of such weak fileds, and the absence of epidemiological data.

General Concluding Discussion

Current Swedish Research

Swedish EMF research has been evaluated by a committee commissioned by the Swedish Research Council. The report concluded that Sweden should contribute with high quality studies in international collaboration and in particular in areas where Sweden has unique resources, such as for long-term epidemiology. The report also concluded that funding

should come through the usual research councils and funding sources, rather than through national research programs supported by the government, which is in contrast to many other countries, e.g. UK, Denmark, France, Switzerland, and Germany, which have established dedicated national research programs. The IEG acknowledges that competitive research groups might be supported through these channels, but that large initiatives would be difficult. The IEG also concludes that projects jointly funded by government and industry are rather difficult to set up in the absence of a national research programme.

Introduction

In this year's report the IEG evaluates some recent data on ELF fields, but the major part of the report is about RF fields and in particular about recent epidemiological studies on disease risk in relation to mobile phone use. Intense research has been ongoing for several years and new results are presented regularly. Yet, the IEG is aware of a number of additional studies that will appear in the next couple of years, particularly from the Interphone study. Therefore it would still be premature to make final assessments, except in some restricted areas. The report also comments on some recent laboratory studies, including genotoxicity, e.g. studies within the REFLEX programme, and important attempts to replicate some earlier neurological findings that had been given considerable visibility. The WHO International EMF project has now been ongoing for ten years and we report on the conclusions from several workshops and environmental health criteria documents that have been produced by this programme.

Extremely Low Frequency (ELF)

Recent biology papers

Genotoxicity

Ivancsits et al. have reported results from several experiments (performed as a part of the European REFLEX programme) in which cultures of human diploid skin fibroblasts were exposed to 50 Hz magnetic fields (up to 2000 μT) for up to 24 h and DNA damage was assessed using the comet assay. Both the neutral (believed to detect only DNA double strand breaks) and alkaline (believed to detect both single strand breaks and double strand breaks, as well as base damage and alkali-sensitive sites) versions of the comet assay were used. In the first study, continuous EMF exposure for 24 h had no effect on DNA strand breaks while intermittent exposure resulted in a significant increase in DNA strand breaks [Ivancsits, et al. 2002]. A dose-response relationship was reported, with statistically significant effects at flux densities ≥70 μT. Various on/off combinations were tested in case of the intermittent magnetic fields, and the maximum effects were found at 5 min on/10 min off. The 5 min on/5 min off intermittency was used in all subsequent studies. In the second study, the maximum effect was seen after 15-19 hours of exposure (1-24 h tested), and the DNA damage appeared to be repaired at 9 h after the termination of exposure [Ivancsits, et al. 2003]. The dose-response was further examined, and significant effects were found at a flux density as low as 35 μT. Cell type specificity was investigated in the third study, and effects were seen in fibroblasts, melanocytes and rat granuloma cells, but not in skeletal muscle cells, lymphocytes or monocytes [Ivancsits, et al. 2005]. The method used the in these studies for quantifying comet tail size (amount of DNA damage) is different from the methods used by other authors. The cells were classified into five categories representing five different degrees of DNA damage, based on visual inspection under microscope. A ‘‘tail-factor’’ was calculated from the classified data for quantitative expression of DNA damage. Because of the fast classification-based method, the authors were able to score 1000 cells per sample (in contrast to the usual 50-100 cells in image analysis). However, only two independent samples were used for each treatment, and the data from these two samples are not reported separately to show the reproducibility of the data. The statistical method thus seems not to be appropriate for the data. Although only two independent samples were available for each treatment (with a single tail factor value calculated from observations on 1000 cells), the results are reported as “mean±standard deviation”, and the authors report they have used Student's t-test and

ANOVA for testing the differences between treatments. No positive controls were used in the experiments. The investigators have used continuously growing cultured cells with cell cycle duration of approximately 30 h. As pointed out recently [Vijayalaxmi and Obe 2005], the presence of normal cycling cells and semi-conservative DNA synthesis during the prolonged exposures could result in increased tail lengths mimicking damaged cells in the comet assay. Thus, the method might not differentiate between true effects on DNA breaks and possible MF effects on cell proliferation, cell cycle and DNA synthesis. The exposure conditions producing maximum strand-break levels (1000 μT, 5 min on/10 min off) were also reported to induce a significant increase of micronuclei and chromosomal aberrations in fibroblasts [Winker, et al. 2005], which can be considered to support the comet assay data. There is no obvious explanation why only the intermittent, but not continuous MF exposure caused genotoxic effects in this study and the other studies by the same group.

In the confirmation study of Scarfi et al. which was also part of the REFLEX programme [Scarfi, et al. 2005], great care was taken to use the same exposure conditions and assay conditions as in the earlier papers of the Austrian group (see above). Clear responses to positive controls (H_2O_2 and mitomycin C) were seen, but no MF effects on DNA strand breaks or micronuclei were observed.

It is not possible at present to conclude whether results from the REFLEX programme indicate the existence of some genotoxic effects from exposure to weak ELF magnetic fields. The failure of the Scarfi group to replicate the Ivancsits results may be due to a flaw in the experimental protocol (in one or both laboratories), or to unknown subtle differences in the protocols or environmental conditions. Additional experiments are needed to resolve the issue.

Luceri et al. used the comet assay to detect strand breaks and oxidated DNA bases in human lymphocytes exposed to a 50 Hz, 1-100 μT magnetic field for 18 hours [Luceri, et al. 2005]. No significant effect on DNA damage was found, but the study had limited ability to detect any effects because of the high variability of DNA damage level. Gene expression profiles of MF-exposed human and yeast cells were also evaluated with DNA microarrays containing 13,971 and 6,212 oligonucleotides, respectively. No MF-related changes in gene expression were found.

Wolf et al. reported increased cell proliferation, changes in cell cycle and increased DNA damage, assessed by the comet assay, in HL-60 leukaemia cells and two fibroblast cell lines exposed to 50 Hz MFs at 500-1000 μT up to 72 hours [Wolf, et al. 2005]. The increase in DNA strand breaks showed two peaks at 24 and 72 h, while no increase was seen at 48 h. A similar time-dependent pattern of DNA damage was observed by measuring 8-OHdG adducts. Involvement of MF effects on free radical species was supported by changes seen in intracellular levels of reactive oxygen species measured by a fluorescent probe, and in the expression of proteins that are involved in redox-mediated signals (NFκB p65 and p50). Also, the MF effects were suppressed by pre-treatment of the cells with the antioxidant α-tocopherol. The results of this study are internally consistent, and effects seen on different endpoints support each other. Independent replication of the key findings would be useful to assess their repeatability.

Lai and Singh reported significantly increased DNA damage in rat brain cells after exposure of the animals to a 60-Hz, 10-μT magnetic field for 24 or 48 h [Lai and Singh 2004]. The same authors have previously reported similar effects after short (2 h) exposure to much

higher magnetic flux densities (100-250 μT). The effect was seen in both the alkaline and neutral versions of the comet assay and, although the size of the effect was relatively small, it was seen in several independent experiments. Exposure for 48 h caused a larger increase than exposure for 24 h. The effects were blocked by treatment with a radical scavenger, a nitric oxide synthase inhibitor and an iron chelator, suggesting involvement of free radicals and iron in the effects of magnetic fields.

Stronati et al. exposed blood samples obtained from five donors to 50 Hz magnetic fields, and evaluated possible genotoxic effects using several genotoxicity endpoints [Stronati, et al. 2004]. The measurements included DNA breaks (comet assay), sister chromatid exchange, chromosomal aberrations, and micronuclei, and the effects of a combined exposure with X-rays were also evaluated. No genotoxic effects were seen after exposure for 2 h at 1000 μT. A small but significant decrease of cell proliferation was reported. Because of the short exposure time, the results are not necessarily inconsistent with the positive findings seen after long-term exposures (described above). The same group conducted another study with the same exposures and endpoints, but using 48 h MF exposures [Testa, et al. 2004]. No significant effects were seen on the genotoxicity endpoints or proliferation. Because of the small study size (n = 4), the data do not provide strong evidence for a lack of effects.

Current overall conclusion on genotoxicity

Studies on genotoxicity are highly relevant in evaluation of carcinogenicity. Studies on genotoxicity of ELF magnetic fields were reviewed by the International Agency for Research on Cancer [IARC 2002], and more recently by Vijaylaxami & Obe [Vijayalaxmi and Obe 2005]. These reviews concluded that there was little evidence of any DNA damage from exposure to MFs alone, except for very strong magnetic fields above 50,000 μT. However, it was noted in the IARC review that several groups had reported findings suggesting that ELF magnetic fields enhance the effects of known DNA-damaging agents such as ionizing radiation. Results from recent studies have not established effects that would change the conclusions of IARC. However, some of the recent studies, in particular within the REFLEX programme, suggest genotoxic effects at low magnetic field intensities (10 μT to 1000 μT) and without combined exposure to known genotoxic agents, but the results are not uniform as another group within the same programme have failed to replicate the data. There is thus a need for a few more investigations on genotoxic effects of ELF to allow for a definitive conclusion.

In vivo cancer studies

Motivated by the epidemiological findings of increased leukaemia risk in children, Sommer and Lerchl investigated the influence of 50 Hz magnetic fields in a mouse strain genetically predisposed to lymphoma [Sommer and Lerchl 2004]. The AKR/J mouse genome carries the AK virus, which leads to spontaneous development of thymic lymphoblastic lymphoma within one year. Groups of 160 female mice were sham-exposed or exposed to 50 Hz magnetic fields at 1 or 100 μT for 24 h per day, 7 days per week, for 38 weeks. There was no effect of magnetic field exposure on body weight gain or survival rate, and the time to lymphoma development did not differ between exposed and sham-exposed animals. The results do not support the hypothesis that chronic exposure to 50 Hz magnetic fields increases the risk of haemopoietic malignancy in this experimental model. However, the relevance of this model to human childhood leukaemia is limited.

Most of the animal studies evaluating possible carcinogenic effects of ELF magnetic fields have been negative. However, a German research group has reported in several separate

experiments that 50 Hz magnetic fields at μT flux densities enhance the development of mammary gland tumours initiated by 7,12-dimethylbenz(a)anthracene (DMBA) in female Sprague-Dawley (SD) rats [Löscher, et al. 1993; Löscher, et al. 1994; Mevissen, et al. 1998; Mevissen, et al. 1996a; Mevissen, et al. 1996b; Mevissen, et al. 1996c; Mevissen, et al. 1993; Thun-Battersby, et al. 1999]. The results were not replicated in similar studies by other research groups in the USA [Anderson, et al. 2000; Boorman, et al. 1999]. In their most recent study [Fedrowitz, et al. 2004], the German investigators tested the hypothesis that the different results are explained by the use of different substrains of SD rats. Exposure to a 100 μT, 50 Hz magnetic field enhanced mammary tumour development in one substrain of SD rats, but not in another substrain obtained from the same breeder. The tumour data were supported by the finding that exposure to MF increased cell proliferation in the mammary gland of the MF-sensitive strain, but no such effect was seen in the insensitive substrain. This finding is potentially important for explaining the inconsistent results, if the substrain-specific effect of MF exposure is confirmed in further independent experiments.

Recent epidemiology paper

Draper and colleagues published results of a large case-control study of childhood cancer risk in relation to residential power lines [Draper, et al. 2005]. They identified 33,000 children from birth to 14 years old who had a cancer diagnosis in England and Wales between 1962 and 1995 and selected one control for each case matched on gender, birth date within 6 months, and birth registration district. The final data set included 9,700 matched case-control pairs for leukaemia who had a known birth address that allowed mapping of distance in relation to transmission lines.

While only a small fraction of homes are close to transmission lines (in this study, 3% were within 600 meters of a 275- or 400-kV transmission line and some of the 132-kV lines), in these homes the line is likely to be the main source of a 50 Hz magnetic field.
They show an elevated relative risk (RR) of leukaemia, based on 64 cases, 1.69 (95% confidence interval 1.13--2.53), for children whose home address at birth was within 200 meters of a high-voltage line compared to those who lived more than 600 m from the line (mainly 275- and 400-kV). For children born in homes located 200 to 600 meters from such a transmission line, the RR was 1.23 (1.02--1.49). They observed no elevated risk of brain tumours, or other cancers.

Given its large size, the risk estimates in the paper should be stable. Furthermore, because contact with the subjects was not necessary, selection bias due to the differential participation among cases and controls, which plagued some of the previous studies [Ahlbom, et al. 2000], was avoided. Despite this, however, the results seem to be dependent on the chosen control group which was noted by the authors, and further explored in a letter to the editor [Kheifets, et al. 2005a]. Kheifets et al. combined all controls into one group and used it for comparison. This approach was justified based on both theoretical and empirical grounds: exposure at birth among controls chosen for leukaemia, brain tumours and other cancers should not depend on the cancer subtype; calculated crude odds ratios did not differ (beyond first decimal) from the matched results presented by the authors of the original paper.

Use of the combined control group revealed a pattern different than the one presented in the original paper. As would be expected, results for all cancers combined showed no relation to the distance. For both leukaemia and brain cancer results at two distances are noteworthy: for the 50-100 meters category an excess of leukaemia and a deficit for brain tumours was observed. For the 500-600 meters category the results showed a modest excess for both

leukaemia and brain tumours. Of note is that the trend reported in the original paper is not present when the combined control group is used, thus indicating that the trend depended on the leukaemia controls rather than on the leukaemia cases. The authors of the original paper emphasise the uncertainty about whether the association represents a causal relation [Draper, et al. 2005]. The IEG notes, however, that distance is known to be a very poor predictor of magnetic field exposure, and therefore, results of this material based on calculated magnetic fields, when completed, should be much more informative.

Radiofrequency (RF)

Recent laboratory studies

Genotoxicity

DNA strand breaks

Previous studies [Lai and Singh 1995; Lai and Singh 1996; Lai and Singh 1997] have reported increased DNA damage, measured by the alkaline and neutral comet assays, in brain cells of rats exposed for 2 h to 2.45 GHz RF (CW or pulsed) radiation at 0.6 or 1.2 W/kg. However, an attempt to confirm part of these results (alkaline comet assay, CW exposure) found no detectable effects [Malyapa, et al. 1998]. The two research groups used different versions of the comet assay, which might be a possible reason for the discrepancy between the results. In a recent study both assay versions were used to investigate DNA damage in the brain cells of rats exposed to pulsed 2.45 MHz RF fields at 1.2 W/kg [Lagroye, et al. 2004]. No effects were observed by either of the methods, suggesting that low-level exposure does not induce DNA damage, and that the different results between the two earlier research groups were unlikely to be due to using different versions of the comet assay.

Two other groups have also reported lack of effects on DNA damage measured by the comet assay. Hook et al. exposed Molt-4 T lymphoblastoid cells to RF fields using four different signals of the type used by wireless communication devices for periods up to 24 h, at SAR levels from 2.4 mW/kg to 3.2 W/kg [Hook, et al. 2004]. The comet assay was used for quantifying DNA damage and the annexin V affinity assay was used to detect apoptosis. No statistically significant differences in the level of DNA damage or apoptosis were observed between sham-treated cells and cells exposed to RF radiation for any frequency, modulation or exposure time. Zeni et al. investigated possible genotoxic effects in human peripheral blood leukocytes following 2 h exposure to 900 MHz radiofrequency radiation [Zeni, et al. 2005]. A GSM signal was used at 0.3 or 1 W/kg. The induction of DNA damage was evaluated using the alkaline comet assay, while structural chromosome aberrations and sister chromatid exchanges were evaluated in lymphocytes stimulated with phytohemagglutinin. Alterations in kinetics of cell proliferation were determined by calculating the mitotic index. Positive chemical controls were also used. No statistically significant differences were observed between the sham-exposed samples and those exposed to RF fields, while significant responses to the positive controls were seen in all cases.

As a part of the European REFLEX project, the investigators who reported increased DNA strand breaks in fibroblasts exposed to ELF magnetic fields also investigated DNA damage in cells exposed to RF radiation, using the classification-based method to quantify DNA damage (tail size) in the comet assay [Diem, et al. 2005]. Cultured human diploid fibroblasts and cultured rat granulosa cells were exposed for 4, 16 or 24 h to 1800 MHz fields with GSM type modulations and SAR levels of 1.2 W/kg (talk-modulation, continuous exposure) or 2 W/kg

(CW continuous exposure, CW and GSM-modulation intermittent exposure- 5 min on/10 min/off). Again, no positive control was used and only two independent experiments were performed. As in the ELF magnetic field experiments, intermittent exposure (5 min on/ 10 min off) was also tested. Increased strand breaks were seen in both the alkaline and neutral comet assays after 16 and 24 h exposures to all signals tested and in both cell types (maximum of 2-fold increase). Intermittent exposure showed a stronger effect than continuous exposure. No significant differences were seen between the 16 and 24 h exposures, and the effect size was similar at 1.2 and 2 W/kg. The methodological limitations of these experiments have been discussed above ("ELF, Recent biology papers", page 6-7).

Mutations

Chang et al. investigated the effects of radiofrequency fields (CW 835 MHz, 4 W/kg, 48 h) on bacterial reverse mutation (Ames assay) and DNA stability (in vitro DNA degradation) [Chang, et al. 2005]. In the Ames assay, RF fields were tested alone or combined with positive chemical mutagens. Some suggestive combined effects with the positive mutagens were reported in the Ames assay, but the findings were not consistent, and the authors concluded that the RF exposure used neither affected the reverse mutation frequency nor accelerated DNA degradation in vitro.

Prenatal exposure to RF fields (2.45 GHz; 10 sec on/50 sec off; SAR in the dam 4.3 W/kg when the field was on, or 0.71 W/kg time-average; 16 h/d on gestation days 0-15) did not affect the mutation rate or the quality of mutations in spleen, liver, brain or testis of 10-weeks-old MutaTM mice (3 animals per group), although exposure was sufficiently intense to induce a slight increase (0.4 to 0.6°C) in the rectal temperature of the exposed dams [Ono, et al. 2004]. Four pregnant females were exposed, and 3 randomly selected male offspring were selected for the mutation analyses. No concurrent control animals were used in the study; the mutation rates were compared to those observed in unexposed animals in previous studies. Because of the small study size and lack of concurrent controls, the study has limited value as evidence for lack of effects.

Micronuclei

Trosic and co-workers [2002-2004] have reported transient changes in both micronucleus (MN) frequency and in counts/proportions of red blood precursor cells in blood and bone marrow of Wistar rats exposed to 2.45 GHz RF fields (CW, SAR 1-2 W/kg: 2 h/day for 2, 8, 15 or 30 days). The same MN data was apparently used in two publications [Busljeta, et al. 2004; Trosic, et al. 2004], so they cannot be considered as independent replications of the finding. Each study consisted of four experiments with ten exposed and six sham-exposed rats in each experiment. The experiments lasted for 2, 8, 15 or 30 days. In the first study [Trosic, et al. 2002], MNs were observed to be significantly increased in peripheral blood after the 8th day of exposure, but not after other exposure durations. In the second study [Trosic, et al. 2004] bone marrow cells were used for evaluating micronuclei. The difference in MN level between exposed and sham-exposed animals was statistically significant only after the 15th day of exposure. The findings may be explained by random fluctuations of MN levels, resulting in significant differences by chance. In any case, the health significance, if any, of this kind of transient changes is unknown.

Current overall conclusion on genotoxicity

Possible genotoxic effects of RF radiation have been of considerable interest because of their potential importance for cancer risk assessment. It is generally accepted that RF radiation lacks sufficient energy to damage DNA directly, but experimental studies are useful in

investigating the possibility of increased DNA damage by indirect mechanisms. The effects of RF fields on many different genotoxicity endpoints have been evaluated both *in vitro* and *in vivo*, and most of the studies have reported no effects [Vijayalaxmi and Obe 2004]. On balance, the recent studies reviewed, including those from the REFLEX programme, do not provide sufficient evidence to conclude that RF fields are genotoxic.

Blood-Brain Barrier (BBB) permeability

One of the major issues related to the health effects of RF radiation has been the potential increase in permeability of the BBB. The findings of the Salford group in Sweden of an increased permeability of the BBB even at low SAR levels have triggered a lot of interest and several replication studies.

The IEG 2003 report stated that "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." The situation is such that, two years later, we know more about the existence of the effect since a major replication study was performed at Brooks in Texas in collaboration with the Salford group. The outcome of that study was reported on at the BioEM05 congress in Dublin in June [McQuade, et al. 2005], but is not yet published. Extensive work on hundreds of animals exposed in the very same exposure system as in Sweden (TEM cells) yielded negative data. Some years ago the Aubineau group in France performed experiments on rats that showed an increase in permeability of the BBB. These data were never published but there is an ongoing replication of this work in the USA.

The recent Japanese work of the Shirai group dealt with young rats (4 and 10 weeks old) which were exposed to the Japanese signal at 1.44 GHz at 2 and 6 W/kg for 90 min/day for 1 or 2 weeks [Kuribayashi, et al. 2005]. Neither BBB related genes (P-glycoprotein, aquaporine-4 and claudin-5) or vascular permeability were affected by exposure and this outcome is most relevant in view of the young age of the animals.

Strong evidence of a lack of effect on the BBB came from the Cassel group in Strasbourg [Cosquer, et al. 2005]. They exposed rats at 2.45 GHz in cylindrical waveguides for 45 minutes and monitored the working memory after whole-body exposure of the animals which had been treated with the scopolamine methylbromide compound which affects memory when it crosses the BBB. However, they found no alteration of the performance and concluded that, in this very sensitive model, exposure did not induce an increase in permeability of the BBB.

In addition, experiments done in vitro on BBB models have been negative [Franke, et al. 2005a; Franke, et al. 2005b]. Improving the assay used in [Schirmacher, et al. 2000], the authors could not reproduce the increased insulin permeability reported earlier.

Overall, while awaiting the results of a few more studies and the publication of the replication of the data of the Salford group, one can conclude today that on balance the evidence of effects of exposure on the BBB at low SAR levels is weak. Recent studies have been better documented in terms of dosimetry and all studies published since the studies of Salford, including confirmation studies, have been negative. This conclusion is in line with that of a recent review by Lin [Lin 2005].

The Salford group had also published on the observation of "dark neurons" or damaged neurons in the brain of rats following acute 2 hour exposures and a delay of 50 days before observation of the damage [Salford, et al. 2003]. There are replications of this study being performed in several laboratories. The outcome of these replication studies will be described in the 2006 report.

Human laboratory studies

Cognitive functions

The most recent pieces of work published on cognitive functions have been the two companion papers of the Haarala and the Preece groups in Finland and UK, respectively [Haarala, et al. 2005; Preece, et al. 2005]. Both studies exposed children to 902 MHz GSM signals in a double-blind manner. In Finland, 32 children (10-14 years old) performed a battery of cognitive tests twice (sham then exposed or vice versa). The tests were the same as in previous work of the same group on adults [Haarala, et al. 2004]. There were no significant differences between the exposure conditions in reaction times and accuracy over all tests. In the UK, 18 children 10-12 years of age were tested using the cognitive drug research cognitive assessment system. The two exposure levels were 0.025 or 0.25 W. There were no significant alterations in any of the tests and in particular in reaction times which had been found to decrease in adults under exposure to more powerful signals [Preece, et al. 1999]. However, there are some experimental weaknesses in these two studies that limit their interpretation, such as low exposure, limited power, and high variability of the tools measuring cognitive function and their applicability to children), although some improvements had been made compared to the previous studies (e.g. blind design).

Another protocol was used by the de Seze group in France on 55 male and female volunteers [Besset, et al. 2005]. One group was exposed to a GSM-900 signal while the other was sham exposed. This double-blind study lasted 45 days during which a neuropsychological battery of 22 tasks screened information processing, attention, memory, and executive function. No effect was found for any of the tests.

In conclusion, recent work on cognitive functions in volunteers exposed to RF fields has been negative in contrast with the various incoherent findings of the previous years (often performed by these same groups).

Cerebral blood flow

In a study of Huber et al. the effects of 900 MHz mobile-telephony signals on regional cerebral blood flow (rCBF) were investigated in 12 healthy male volunteers [Huber, et al. 2005]. The positron emission tomography (PET) technique was used to monitor rCBF in the brain. Two types of exposure were used: base-station-like and mobile phone-like. The exposure of one side of the head lasted 30 min (1 W/kg averaged over 10 g). Following exposure, an increase in rCBF was observed in the dorsolateral prefrontal cortex on the side of exposure. It is remarkable that only the mobile phone-like exposure elicited the effects on rCBF. The authors interpreted this finding as supporting their previous observations that only pulse-modulated RF (as in the mobile phone-like signal, in contrast with the continuous base-station-like signal) is necessary to induce changes in brain physiology. However, changes in rCBF are not by themselves an indication of health damage. Based on the studies by Huber et al. [Huber, et al. 2002] and Haarala et al. [Haarala, et al. 2003], one can conclude today that it is possible that there is an influence of RF exposure on rCBF, although these changes are within the range of normal variability. The role of modulation of the RF signals in the elicitation of these effects is thus still open.

Hearing
Following all of the recent publications and in particular those originating from the European Commission GUARD programme on hearing, one can now conclude about the absence of effects of RF exposure due to cellular phones at GSM frequencies, on the main parameters of the auditory system. However, there is still one European Commission research project ongoing on cellular phone exposure at UMTS frequency, with reports due by 2007.

Several specific and review papers were given at BioEM05 in Dublin. They all converged towards an absence of effects of RF fields on various parameters of the hearing track. Within the GUARD programme, Galloni et al. had found no alteration of distortion products of otoacoustic emissions in rats [Galloni, et al. 2005] and Parazzini et al. made the same observation in humans [Parazzini, et al. 2005].

As part of a collaborative effort of French teams within the French COMOBIO programme, Maby et al. recorded auditory evoked potentials in healthy and epileptic patients exposed to mobile phone emission [Maby, et al. 2005]. They found no difference among the groups except for a minor alteration of some correlation coefficients which the authors could not relate to any health effect.

Sleep
There are continuing investigations of the effects of RF exposure on sleep. In 2004, Mann and Röschke reviewed the published data and concluded that there is some evidence for a slight sleep promoting effect and an increase of the alpha power of the sleep EEG [Mann and Röschke 2004].

More recently, an Australian group has reported minor effects on REM sleep (dream phase) following exposure of volunteers to mobile phone signals at moderate level for 30 min [Loughran, et al. 2005].

It can be concluded today that there may be alterations of sleep caused by exposure, but the data are still inconsistent. Moreover, there is no known effect on health attributable to these low-amplitude alterations of sleep.

Recent epidemiological studies

Mobile phone studies

Acoustic neuroma and brain tumours in the Interphone study
In the international collaborative Interphone study, the first national reports on acoustic neuroma were published 2004 from Sweden and Denmark [Christensen, et al. 2004; Lönn, et al. 2004a], and were reviewed in last year's report. During 2005, these two countries have published results also on brain tumours. A first international joint analysis has also appeared and more are expected within a year. These new studies are discussed below.

A Danish study of glioma and meningioma [Christensen, et al. 2005] was based on cases aged 20-69 years and prospectively identified from five neurosurgery departments during September 2000-August 2002. A total of 464 gliomas were identified, of whom 354 were eligible and 252 (71%) interviewed. Similarly, 291 meningioma cases were identified, 238 were eligible and 175 (74%) interviewed. Controls were identified from the Population Registry using 1:1 frequency matching. Among controls, a response rate of 64% was

achieved. The proportion of exposed subjects (regular mobile phone users, i.e. had used a mobile phone on average at least once per week for 6 months or more) was 42% gliomas, 38% meningiomas and 47% among controls. For low-grade gliomas, a slightly increased risk was associated with use starting at least 10 years earlier, although with wide confidence intervals (OR=1.6, 95% CI 0.4-6.1) while for high-grade gliomas, a reduced risk was indicated (OR=0.5, 95% CI 0.2-1.3). In terms of cumulative hours of use, no clear trend was found for either low or high grade tumours. For meningioma, no relationship with time since starting mobile phone use (OR=1.0 for ≥10 years) was found.

A Swedish study of glioma and meningioma [Lönn, et al. 2005] was conducted with Umeå, Stockholm, Göteborg, and Lund regions as the study area. Cases diagnosed between September 2000 and August 2002 were identified from hospitals and cancer registries and had to be aged 20-69 years at diagnosis. Controls were identified from the national Population Registry. Participation among glioma cases was 74% (N=371), meningioma 85% (N=273) and controls 71% (N=674). Proportion of regular mobile phone users was 42% among gliomas, 43% meningiomas and 59% controls. Regular use of mobile phones was not associated with either tumour type (OR=0.8, 95% CI 0.6-1.0 for glioma and OR=0.7, 95% CI 0.5-0.9 for meningioma. No association was found with time since starting mobile phone use overall (OR=0.9, 95% CI 0.5-1.6 for ≥10 years) or for analogue or digital phones. Similarly, time since starting or cumulative hours of use were not associated with meningioma. No association was found for laterality of use (OR=1.1, 95% CI 0.8-1.5 for ipsilateral use in glioma, OR=0.8, 95% CI 0.5-1.1 for meningioma). A slightly increased risk of glioma was observed for ipsilateral use with at least 10 years duration, although with wide confidence intervals. A decreased risk on the contralateral side for the same duration of use indicates, however, that this result may have been influenced by recall bias. Furthermore, the risk increase was not apparent for the lobes receiving the highest exposure, which further strengthens the hypothesis that recall bias may have affected these results.

A study using data published previously from Sweden and Denmark as well as cases and controls from Finland, Norway, and the UK [Schoemaker, et al. 2005] included 678 cases of acoustic neuroma and 3553 controls. Of the eligible cases 83% participated and 51% of the controls were successfully interviewed. Regular use of mobile phones was reported by 53% of the cases and 54% of the controls. No increased risk was found for regular mobile phone use (OR=0.9, 95% CI 0.7-1.1). Acoustic neuroma was not associated with the time since first regular mobile phone use or cumulative years of use. No increased risk was associated with the cumulative number of calls or cumulative hours of use. Risk of acoustic neuroma was not increased on the side were the phone was predominantly held (ipsilateral use/tumour). However, an increased risk of ipsilateral tumours was found for more than 10 years of use (OR=1.8, 95% CI 1.1-3.1). The authors interpreted their findings cautiously, emphasizing the overall lack of association and mentioned both bias and true effect as possible explanations for this finding.

Interphone studies represent a new generation of studies on possible risks related to mobile telephony, which provide new information on this rapidly growing and already extremely prevalent exposure. Among the strengths are large and carefully planned international efforts with emphasis on case definition and ascertainment, exposure assessment and quality control. Nevertheless, some limitations remain. Exposure assessment relies on self-reported mobile phone use and therefore is susceptible to recall bias. Selection bias may be introduced due to low participation rates among controls in some of the centres, since participating controls appear to be more likely to be phone users. There are also still limitations regarding the length

of the latency period that can be studied for this new exposure. In the studies published so far, results are negative for brain tumours and inconsistent for acoustic neuroma, for which there is a suggestion for an increased risk among long-term users. Interpretation of the acoustic neuroma results at present is difficult: if the increase is due to recall bias, it is unclear why it would be present for acoustic neuroma only and not operate for brain tumours. Acoustic neuroma is a slowly growing and non-fatal tumour, thus it is possible that it is being diagnosed more often among cell phone users as they experience loss of hearing (detection bias). However, this explanation is not entirely satisfactory as it is unclear as to why such a bias would be present for long-term users only and why it would not have been visible already in nation wide descriptive data.

Other studies on acoustic neuroma and brain tumours

A Swedish study [Hardell, et al. 2005b] used data from an earlier study [Hardell, et al. 2002a] with 1429 cases diagnosed 1997-2000 and 1470 population-based controls to assess differences in risk associated with use of mobile phones in urban and rural settings. The rationale for these analyses is that mobile phones on average use a higher output power level when transmitting in rural areas where base stations are sparse, as compared to urban areas where base stations are more densely situated [Lönn, et al. 2004b]. This would lead to higher levels of RF exposure to the head when mobile phones are used in rural areas. For all brain tumours combined, higher risk estimates were found in rural than urban areas, regardless of latency period used. However, the precision in the risk estimates is compromised because of small numbers. The finding was most pronounced for digital phone use, although a similar pattern was observed also for analogue and cordless phones. For the latter type of phone the base station is placed inside the home or office and therefore no difference in the risk estimates between urban and rural areas would be expected.

The same group has also assessed risk of brain tumours by age based on the same material as described above [Hardell, et al. 2004b]. No consistent trend was found. Instead the highest OR's tended to be among the youngest age group (20-29 years), followed by the oldest. The numbers of cases and controls in these age groups were, however, too small to provide meaningful information. No direct analysis of whether or not the relative risks differed across age groups was presented in the paper.

The Hardell group has also published results based on a new material with malignant brain tumours diagnosed in 2000-2003 [Hardell, et al. 2005c]. This is the third material collected by this group. Malignant brain tumours from the Uppsala/Örebro and Linköping areas were identified from the regional cancer registries. As in previous studies by this group, deceased patients were excluded (187 malignant and 18 benign tumours). In addition, 70 patients were excluded for other reasons (not specified whether malignant or benign). Out of 359 contacted malignant cases, 317 participated (88%). Controls were identified from Population Registry with frequency-matching on age and sex. In total, 692 controls participated (84%). Exposure assessment was based on similar methods as in earlier studies, i.e. a mailed questionnaire with supplementation of answers over the telephone. In addition, all cases and controls were also interviewed over the phone to "verify exposures and get additional detailed information". In the data analysis with unconditional logistic regression, adjustment for age, sex, SES, and year of diagnosis was used. Of the cases 66% had used a mobile phone (21% had used analogue and 62% digital phones). The corresponding figure for controls was 51% (11% analogue and 50% digital). The report does not mention any requirement in terms of amount of use needed to be regarded as a mobile phone user (i.e. could be as little as one phone call). For all malignant tumours, use of both analogue and digital phones (with >1 yr latency) was

associated with approximately two-fold risk (OR for analogue phones 2.6, 95% CI 1.5-4.3 and for digital phones 1.9, 95% CI 1.3-2.7). Slightly higher risk estimates were found for astrocytoma than other malignant tumours (OR 2.9 for analogue and 1.9 for digital phones relative to 1.6 and 1.9 for other cancers). Increased risks were found already after 1-5 years of using a digital phone (OR=1.6, 95% CI 1.1-2.4) and a cordless phone (OR=1.8, 95% CI 1.2-2.8), although risk estimates were highest after more than 10 years latency (OR for analogue phones 3.5, 95% CI 2.0-6.4), for digital phones 3.6, 95% CI 1.7-7.5, and cordless phones 2.9, 95% CI 1.6-5.2). These findings differ somewhat from earlier results on malignant brain tumours reported by this research group. The two previous studies found risk estimates close to unity when using a one year latency period [Hardell, et al. 2002b; Hardell, et al. 1999], or 1-6 years latency period [Hardell, et al. 2002b], whereas the newly reported study found increased risks also after a very short period of exposure. In previous studies risk increases for shorter latency periods were confined to subgroups of users. As in earlier reports, highest risks were found for analogue phones and an increasing trend with latency was indicated. However, risk estimates were substantially higher than in earlier publications.

Data on meningioma and acoustic neuroma were also included in the most recent study by Hardell and colleagues, published in a separate paper [Hardell, et al. 2005a]. The study included 305 cases with meningioma, 84 with acoustic neuroma, and 692 controls (the same controls were used as in the study described above). The response rates are reported as 89% for cases and 84% for controls. Cases were only included when histopathological diagnosis became available and if they were alive at that time. As in the previously described work, exposure information was collected by a questionnaire and supplemented over telephone. Case/control status was not disclosed to the interviewer by the investigators. For acoustic neuroma the strongest effect estimates are reported for analogue phone use, with an overall OR=4.2 (95% CI 1.8-10). For >15 years of use the OR=8.4 (95% CI 1.6-45). There are also substantial excess risks for 1-5 years (OR=9.9; 95% CI 1.4-69), 5-10 years (OR=5.1; 95% CI 1.9-14), and for >10 years latency (OR=2.6; 95% CI 0.9-8.0). The laterality analyses are based on >1 years of use. For use of phone at same side as the tumour the OR=5.1 (1.9-14) and for use on opposite side the OR=4.9 (1.2-21). For meningioma, the authors found elevated risks that increased with duration of use, particularly for analogue phones. The association, however, is weaker than for acoustic neuroma and the internal consistency is less obvious.

While the Hardell study taken at face value appears to support the recent Swedish Interphone study results on acoustic neuroma [Lönn, et al. 2004a], several considerations call for a cautious interpretation. First, looking at table 2 [Hardell, et al. 2005a] it appears that current users of digital phones (> 1 year) in the controls are 50%. At the same time the nation wide number of subscriptions per person is increasing from 71 to 95% during the study period. One person can have multiple subscriptions, but this is most likely offset by the fact that the denominator includes also the very young and the very old. In the Swedish Interphone study over 90% of the controls answered yes to the question if they had ever used a mobile phone (Lönn, personal communication), and 59% reported that they had used a mobile phone *regularly*, i.e. on average at least once per week during six months or more [Lönn, et al. 2005]. For the corresponding calendar period and age group the proportion of mobile phone users among controls in the latest Hardell et al study was 55% (Hardell, personal communication), but with no requirements regarding the amount of mobile phone use needed to be classified as a mobile phone user. Second, Hardell et al. obtain considerable OR elevations even for the shortest latency periods of 1-5 and 5-10 years, which is remarkable for this type of slow growing tumour. The concern is amplified by the fact that cases are only

included after the histopathological diagnosis has become available. The problem is that this may happen several years after the clinical diagnosis has been made. As a consequence a substantial proportion of the exposure may have taken place after symptoms have occurred. Third, the laterality analyses give no, or weak, support for the notion that the risk is higher on the exposed side of the head. For the malignant tumours a large proportion of the cases have died prior to being identified for inclusion in the study, and were therefore excluded.

The Hardell group's results are potentially important because they differ from those of other research groups (see Table 1 and 2). It is noteworthy that they differ also for shorter latency periods where most available studies have sufficient precision for adequate analysis.

Mobile phone studies on other tumours

The Hardell group has also assessed the risk of salivary gland cancer in relation to mobile phone use [Hardell, et al. 2004a]. The cases were identified from regional cancer registries in entire Sweden 1994-1999/2000 and included malignant tumours only, with deceased cases excluded (N=96). Of the eligible cases 66% participated. Controls were from the brain tumour study, with participation of 89%. Exposure assessment was as in the brain tumour studies of the same study group. Of the cases, 12% had used analogue phones and 17% digital phones. For controls, the proportions were 11% and 16%. No increased risks were found for either analogue (OR=0.9, 95% CI 0.6-1.5) or digital phone use (OR=1.0, 95% CI 0.7-1.5). In the analyses by anatomic location, a non-significantly increased risk was found for the submaxillary gland (OR=1.4, 95% CI 0.6-3.5 for any phone use), but not for the parotid (OR=1.0, 95% CI 0.7-1.4) or other locations (OR=1.1, 95% CI 0.5-2.7). Participation among cases was much lower than in other reports by this group.

Also a study on mobile phone use in relation to non-Hodgkin lymphoma has been presented by this group [Hardell, et al. 2005d]. The cases aged 18-74 years with diagnosis in 1999-2002 in Umeå, Örebro, Linköping, and Lund areas were recruited from regional cancer registries. Of the 1163 cases ascertained, 910 (78%) were included in the study. A total of 1108 controls were identified from the Population Registry with frequency-matching by age and 1016 (92%) of them participated. Mailed questionnaires with follow-up interviews by phone were used for exposure assessment. Mobile phone use was reported by 59% of controls and 55% of cases. For 819 B-cell lymphomas, no increased risks were found for digital or analogue phone use regardless of latency (OR 1.0 for analogue and 1.1 digital phones). For 53 T-cell lymphomas, non-significantly increased risks were reported (OR 1.5, 95% CI 0.5-4.3 for analogue and 3.0, 95% CI 0.3-34 for digital phones with 10-year latency). No dose-response relationship with cumulative hours of use was found. This study contributed little evidence for or against an association of lymphoma with mobile phone use.

Methodological studies

Exposure assessment

Several validation studies have been conducted assessing the accuracy of reported mobile phone use. All studies have been based on volunteers and a short recall period (six months in most studies). Self-reported use has been compared with a more objective information source such as operator data or data collected by the mobile phone.

A study conducted in the UK [Parslow, et al. 2003] used 93 volunteers recruited through advertisements over a study period of six months. Mobile phone use reported in postal questionnaires was compared with operator records. Information was collected at the end of the usage period, i.e. the subjects had to recall their phone use during the last six months.

Only out-going calls were analysed as not all operators were able to provide data on in-coming calls. For number of calls, a reasonable agreement was found (κ=0.39, r=0.48). Slightly better agreement was reported for total duration of calls (κ=0.50, r=0.60). However, there was substantial over-reporting of both numbers of calls (by a factor of 1.7) and duration of calls (by a factor of 2.8).

A German study [Samkange-Zeeb, et al. 2004] was based on 68 subjects (volunteers and subscribers randomly selected from phone book). Interview data were compared with operator records, obtained at the end of the three-month study period (recall period). A moderate correlation was found between the two sources of information. The mean number of calls per day was reported as 1.0 vs. 1.3 in the operator records and mean duration of call 2 min vs. 1.4 min (r=0.62 for number of calls and 0.34 for duration). The cumulative calling time during the monitoring period was 3.2 hours vs. 3.1 hours (r=0.56 for total duration of calls, kappa 0.34).

Another German study [Berg, et al. 2005] recruited 45 volunteers and contrasted interview data with that recorded by software-modified phones provided for the participants. The special phones were used for one month, while interview pertained to a three-month period and was performed at the end of the monitoring period. For number of calls, the ratio of reported to recorded was 0.71 with a moderate correlation (r=0.48). For total duration of calls, the ratio of reported to recorded was 1.14 with a similar correlation for number of calls (r=0.48).

These three studies indicate that measurement error in self-reported mobile phone use is substantial, even for short-term recall. If this error is non-differential (e.g. similar for cases and controls), it is likely to bias risk estimates towards the null. Yet, none of the studies have addressed potential differences between cases and controls (recall bias).

Selection bias

A Finnish study [Lahkola, et al. 2005] assessed selection bias in the Finnish Interphone study. The subjects were 103 cases and 321 controls, who refused to participate in the full interview, but gave a short telephone interview. Among both cases and controls, refusers had used mobile phones less than participants. The proportion of regular users was 10 percentage points lower among non-participants than participants in both groups (83% vs. 73% among controls and 76% vs. 64% among cases). Use of mobile phone was also assessed from a database among subjects who declined even the short interview. Complete refusers had used mobile phones even less than those who gave a short interview.

A similar pattern was found in the Swedish Interphone study [Lönn, et al. 2004a], where 16% of the non-participating controls answered a few questions about their mobile phone use over the phone. The proportion of regular mobile phone users (at least once per week) among the non-participants was 33% compared to 59% among participating controls. Note, however, that the questions were answered by only a small proportion of the non-participants, and they were not a random sample from this group; these were persons who could be reached by telephone. It is possible that the proportion of mobile phone users is higher among the non-participating controls that could not be reached over the phone, as this might be persons who are seldom at home, and therefore perhaps more likely to have a mobile phone.

The findings suggest that it is important to evaluate the possibility of selection bias. If such distortion is found, it may have to be taken into account in the analyses and interpretation of studies. Selection bias might be one possible explanation for the reduced risk estimates

observed in several of the studies. Combination of different sources of error (random error, information bias and selection bias) may complicate the epidemiological studies on the subject more than has been anticipated.

Current overall conclusion on mobile phone use

On balance the currently available evidence suggests that for adult brain tumours there is no association with mobile phone use for at least up to, say, ten years of use. For longer latency the majority of the evidence also speaks against an association, but the data are still sparse. The same conclusion holds for short-term use and acoustic neuroma. However, for long-term use and acoustic neuroma there is a concern, and more information is required. Furthermore, studies of children are yet to be done, as well as studies on outcomes other than cancer.

Recent studies on transmitters

The IEGEMF reviewed existing studies on health risks in populations around transmitters in its first annual report [IEGEMF 2003]. Since then two new studies from Korea have been published [Ha, et al. 2003; Park, et al. 2004]. Both these papers present ecological data in which cancer morbidity and mortality rates are calculated in regions that include AM radio transmitters of over 100 kW and in control areas without such broadcasting towers. Although there are some elevated rates in the data, the authors point out several methodological limitations that must be considered when evaluating these results. These are quite relevant issues and at the time being the results cannot be interpreted in the context of an association between environmental RF exposure and cancer risk. The conclusions from the authors themselves are that further data are needed and that proper analytical designs are required to explore this further.

The first report on cancer risks in people living near mobile phone base stations has recently been published [Wolf and Wolf 2004]. This is a study on a small population of 622 people in a neighbourhood in Israel where a base station was erected in 1996. Information about cases of cancer during a one year period from 1997 to 1998 was obtained from an outpatient clinic that served the area. Comparisons were made with a similar neighbourhood without base station and with national rates. While the calculated rates are higher than those in both the comparison neighbourhood and the nation rates, the findings are indeed inconclusive. The diagnostic panorama looks very much like the one that might be expected from a small population of this age composition. For none of the cancer sites was the numbers sufficient for analysis. To what extent cases are completely assessed from the local clinic is not discussed. The very brief induction period makes it particularly difficult to link the cancer rates to the RF exposure. A study on an environmental RF exposure and cancer risk can not meaningfully be planned on a 622 people population followed for one year. The study does not meet normal methodological standards. For example, the possibility of confounding by demographic factors is assessed by chi-square test and t-test, procedures that do not address that issue.

WHO International EMF programme

Environmental Health Criteria document on Static fields

The following is a summary of the WHO Static Fields EHC document [WHO 2005]. Static electric fields occur naturally in the atmosphere. Values of up to 3 kV/m can occur under thunderclouds, but otherwise lie in the range 1–100 V/m in fair weather. The next most common cause of human exposure is charge separation as a result of friction. For example,

charge potentials of several kilovolts can be accumulated while walking on non-conducting carpets, generating local fields of up to 500 kV/m. Direct current (DC) power transmission can produce static electric fields of up to 20 kV/m, rail systems using DC can generate fields of up to 300 V/m inside the train, and VDUs create electric fields of around 10 - 20 kV/m at a distance of 30 cm.

The geomagnetic field varies over the Earth's surface between about 35 - 70 μT. Man-made static magnetic fields are generated wherever DC currents are used, such as in some transportation systems powered by electricity, industrial processes such as aluminium production and in gas welding. Magnetic flux densities of up to 2 mT have been reported inside electric trains and in the development of magnetic levitation (MagLev) transport systems. However, the largest static magnetic fields likely to be experienced by members of the public occur when they are exposed as patients to fields generated by Magnetic Resonance Imaging (MRI) systems during clinical diagnostic procedures. These are usually in the range of 0.2 – 3 T although higher magnetic fields up to 9.4 T are used for whole body patient scanning in some research applications.

There are no good long-term studies of the possible long-term health effects of exposure to static electric or magnetic fields. Epidemiological studies have focussed almost exclusively on workers exposed to static magnetic fields of up to several 10's mT either as welders, aluminium smelters, or workers in various industrial plants using large electrolytic cells in chemical separation processes. However, such work is also likely to have involved exposure to a variety of potentially hazardous fumes and aerosols, thus confounding interpretation. In general, so few animal studies have been carried out with regard to genotoxicity and cancer that it is not possible to draw any firm conclusions. In addition, there are no good epidemiological studies of reproductive and developmental outcome following exposure to strong magnetic fields such as those used in MRI. Most animal studies show no effect, but data are sparse concerning the possible effects of exposure above 1 T.

A number of acute effects, however, are known to result from even transient exposure to static fields at high field strengths and flux densities. Static electric fields do not penetrate the human body; it induces a surface electric charge. A sufficiently large surface charge density may be perceived through its interaction with body hair and by other effects such as spark discharges (microshocks). The perception threshold in people depends on various factors and can range between 10 - 45 kV/m. Annoying sensation thresholds are probably equally variable, but have not been systematically studied.

Physical movement within a static field gradient induces electric fields in the body and sensations of vertigo and nausea, and sometimes phosphenes and a metallic taste in the mouth, for static fields in excess of about 2 - 4 T. Similarly, aversive responses can be induced in freely moving laboratory animals exposed to static magnetic fields of 4 T and above. Although only transient, such effects may adversely affect people. Together with possible effects on eye-hand co-ordination, the optimal performance of workers executing delicate procedures (e.g. surgeons) could be reduced, with a concomitant impact on safety. Cardiovascular responses, such as changes in blood pressure and heart rate, have been occasionally observed in human volunteer and animal studies. However, these were within the range of normal physiology for exposure to static magnetic fields up to 8 T. However, as a result of Lorentz forces exerted by static magnetic fields on moving charge carriers, the flow of blood induces electrical (flow) potentials and currents around blood vessels, particularly around the heart and major arteries. Although not experimentally verified, calculations

suggest three possible effects: minor changes in heartbeat (which may be considered to have no health consequences), the induction of ectopic heartbeats (which may be more physiologically significant), and an increase in the likelihood of re-entrant arrhythmia (possibly leading to ventricular fibrillation). The first two effects are thought to have thresholds in excess of 8 T; threshold values for re-entrant arrhythmia are more difficult to assess.

National authorities are recommended to implement programs that protect both the public and workers from any untoward effects of static fields. However, given that the main effect of static electric fields is discomfort from electric discharge to tissues of the body, the protective program could merely be to provide information on situations that could lead to exposure to large electric fields and how to avoid them. A program is needed to protect against established acute effects of static magnetic fields. Because sufficient information on possible long-term or delayed effects of exposure is currently unavailable, cost-effective precautionary measures such as those being developed by WHO (www.who.int/emf) may be needed to limit the exposures of workers and the public.

Recommendations for further research were also made. However, there appears to be little benefit in continuing research into the health effects of static electric fields. None of the studies conducted to date suggest any untoward health effects, except for possible stress resulting from prolonged exposure to microshocks. Thus, there are no recommendations for further research concerning biological effects from exposure to static electric fields. In addition, there is only limited opportunity for significant exposure to these fields in the workplace or living environment and this therefore does not warrant any epidemiological investigation.

With regard to static magnetic fields, it was considered that research carried out to date has not been systematic and has often been performed without appropriate methodology and exposure information. Co-ordinated research programs are recommended as an aid to a more systematic approach. There is also a need to investigate the importance of physical parameters such as intensity, duration and gradient on biological outcome. Specific research recommendations covering epidemiology, volunteer studies, animal and *in vitro* biology, studies into mechanisms of interaction, and theoretical and computational investigations are also given on the WHO website.

WHO Workshops

Publication from Istanbul workshop: Childhood Sensitivity to EMFs

With the rapid advances in EMF technologies and communications, children are increasingly exposed to electromagnetic fields (EMFs). A two-day international workshop was held in Istanbul in June 2004 which addressed the possible sensitivity of children to such exposure. The Workshop was organized and cosponsored by WHO, SSI, the European Commission Coordinated Action (EMF-NET), the Electric Power Research Institute (EPRI), European Cooperation in the Field of Scientific and Technical Research (COST 281), the Research Association for Radio Applications (FGF), International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the Medical Faculty of Gazi University (Turkey). The output of the workshop has been summarised by Kheifets et al [Kheifets, et al. 2005b] and individual papers presented at the workshop have been published in a supplement to Bioelectromagnetics (2005, volume 26, supplement 7).

Two particular issues addressed at the workshop were the association between childhood leukaemia and exposure to power frequency magnetic fields, mentioned above, and the possible effects of radiofrequency fields from mobile telephony on the developing central nervous system (CNS), first raised by the Stewart Report [IEGMP Independent Expert Group on Mobile Phones (Chairman: Sir William Stewart) 2000]. With regard to the latter, the major changes to the CNS during infancy, childhood and adolescence comprise maturation of the 'hard-wiring', namely increased myelination, facilitating the transmission of information, occurring rapidly over the first 2 years but extending into the second decade of life, and remodelling of the synaptic connections between neurons, which occurs after the first two years and continues through into adolescence, mostly by synapse elimination as 'redundant' connections are lost. With regard to the formation of new synapses, spontaneous and stimulus-evoked electrical activity in the CNS is believed to play a crucial role. Whether radio frequency fields could affect these processes is not known, but few small neurobehavioral studies in volunteers, including children, and in animals have not reported robust responses to RF exposures associated with mobile phones.

In summary, there were clear biological and dosimetric differences between children and adults, some of which persist into adolescence, but there is no good evidence that children are more susceptible to radiofrequency (RF) fields than adults, but little research has specifically addressed potential vulnerability and health effects in children. At power frequencies, an increased risk of childhood leukaemia has been found to be consistently associated with exposure to environmental levels of magnetic fields very much below present guidance values. There is currently no scientific explanation for this association, although two hypotheses for such an effect, namely the flow of 'contact' electric currents through the bone marrow of children, and the disruption of nocturnal melatonin secretion children exposed to weak power frequency magnetic fields, were discussed at the workshop.

A series of specific research recommendations focussing on childhood exposure to EMFs were made at the workshop and are available at the WHO website (www.who.int/emf).

WHO workshop on base station exposures

A workshop was recently organised by the EMF project of WHO that dealt with potential health effects of base stations of mobile telephony and other networks. The slides of the various speakers are available on the Website of WHO (www.who.int/peh-emf/meetings/base_stations_june05/en/index.html) and papers will be published soon.

RF exposure from bases stations and other transmitters is generally low. Indeed, it is three orders of magnitude or more below the exposure experienced from the telephones themselves. Even considering that transmitter exposure is of longer duration than exposure from phones and involves the whole body, it is very weak. This has to be factored in when assessing possible health risks. In addition to this, the few studies that exist on health risks in population around base stations and other transmitters have experienced difficulties with exposure characterization and, particularly the cancer studies have also limitations because of small numbers of cases.

The conclusions of this workshop was that there are no known risks associated with these RF sources but that the fears related to exposure to the base stations have to be dealt with at various levels by informing the public and local authorities and addressing the concerns of the people who report to be hypersensitive. One of the main conclusions that was reiterated is that

there is no evidence of a causal relationship between exposure and subjective symptoms in people who claim to be hypersensitive, as was also concluded at the WHO workshop on electrical hypersensitivity in Prague, 2004. The research recommendations from the base station workshop will be combined to those on RF from other workshops and published by WHO before the end of the year 2005.

General concluding discussion

Update on key issues

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

a. The possibility that some individuals are particularly sensitive and react with symptoms to exposure to EMF has been discussed in a previous report [IEGEMF 2004] and also at a WHO workshop (WHO International Seminar and Working Group Meeting on EMF Hypersensitivity, http://www.who.int/peh-emf/meetings/hypersensitivity_prague2004/en/index.html). While these symptoms are very real and some subjects suffer severely, there are hardly any data that suggest that EMF exposure is a causal factor.
b. The few studies that have been published on health risks among populations living near transmitters have had major methodological shortcomings [IEGEMF 2003; IEGEMF 2005 (current report)]. However, the exposure to the general population that results from transmitters is very weak and one would not expect such exposure to produce a health risk as discussed in the previous report [IEGEMF 2003]. Indeed, one would assume that if RF exposure at low levels is associated with a health risk it would be considerably easier to detect it in studies of mobile phone users, or highly exposed occupational groups. The overall conclusion is that exposure from transmitters is unlikely to be a health risk.
c. Studies of cancer risk in mobile phone users have been discussed in all reports [IEGEMF 2003; IEGEMF 2004; IEGEMF 2005 (current report)]. Short-term use of mobile phones does not appear to be associated with cancer risks in adults. However, other outcomes have not been studied, no studies on children or adolescents have been done, and long-term use has not been fully evaluated. In particular for acoustic neuroma there is a concern about long-term mobile phone use.
d. For power frequency fields only limited data have been published in recent years which has been discussed in several reports [IEGEMF 2004; IEGEMF 2005 (current report)], and the previous assessment by IARC remains unchanged, namely that such fields are a possible human carcinogen. WHO recommended in its recently finalized ELF Environmental Health Criteria document (not yet published) that implementing very low cost precautionary procedures to reduce exposure is reasonable and warranted.
e. High exposure to static magnetic fields occurs for example near MRI machines. Very little data exist for risk assessment related to long-term exposure to static fields [IEGEMF 2005 (current report)].

Upcoming or newly published reviews

A report on “mobile telephony and health” was commissioned by the French “Health and Environment Agency” (AFSSE) to an expert group. The document was published in French and English in April 2005 (www.afsset.fr) along with the opinion of the Agency. The report gives an extended update on the mobile telephony and related wireless networks, on the

research on biological and health effects and gives recommendations for risk communication, management and research. It is the most recent comprehensive report of its kind.

The UK Independent Advisory Group on Non-Ionizing Radiation (AGNIR) has reviewed the evidence concerning possible relationships between residential and/or occupational exposure to power frequency electromagnetic fields (EMFs), the suppression of the normal nocturnal elevation of plasma melatonin levels, and the incidence of breast cancer [AGNIR In press]. Three specific issues were addressed, namely: whether EMFs can affect the production or action of melatonin; whether melatonin can affect the risk of breast cancer; and whether exposure to EMFs affects the risk of breast cancer. The report is in press, but was not published in time for a fuller description here.

Status of bioelectromagnetics research worldwide

Research in "bioelectromagnetics" has been very active in recent years, motivated by health concerns related to mobile telephony. Most of the research activity was in Europe, with Japan, Korea and Australia being also active. A large part of the programmes have been at the international level (e.g. EC 5th FP) or at the national level ("LaVita" in Finland, MTHR in the UK, etc.). This is bound to continue in view of the need for further international cooperation, large research budgets and coordination at the international level by WHO.

Research on effects of ELF exposure has been steadily decreasing and the emphasis today, besides wireless communication, is with therapeutic applications of EMF.
The overall quality of the research has steadily risen: exposure systems are now of sufficient quality and modelling of the EMF levels inside the tissues and organs or the culture media has greatly improved. Often replication or conformation studies have been performed with the help of the original investigators. In conclusion this field of science, led by health concerns, has matured and the fact that non- specialized scientific journals now publish negative as well as positive findings is a sign of that evolution. Another trend is that of the creation of national or trans-national foundations with the purpose of funding the research with contributions from governments and industry and setting up of scientific boards and firewalls. This is helping increase the independence of the research and its acceptance by the public.

Current Swedish research

Swedish EMF research was evaluated by a committee commissioned by the Swedish Research Council [Vetenskapsrådet 2004]. The report concluded that Sweden should contribute with high quality studies in international collaboration and in particular in areas where Sweden has unique resources, such as long-term epidemiology. The report also concluded that funding should come through the usual research councils and funding sources rather than through national research programs supported by the government. The IEG acknowledges that competitive research groups might be supported through these channels, but that large initiatives would be difficult. The IEG also concludes that projects jointly funded by government and industry are rather difficult to set up in the absence of a national research programme or specific foundation. It is therefore with some relief the IEG notes a proposal that the SSI obtains 1 million Euro for 2007 for research related to radiation protection. However, considering the fact that this funding must support the entire radiation protection area detracts from the relief.

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Table 1. Results for epidemiological mobile phone studies of brain tumors:

	Brain tumors		**Brain tumors, short latency**		**Brain tumors, longer latency**	
	No. exp cases	RR (95% CI)	No. exp cases	RR (95% CI)	No. exp cases	RR (95% CI)
[Hardell, et al. 1999]	78	1.0 (0.7-1.4)	78	1.0 (0.7-1.4) >1 yr	34 16	0.8 (0.5-1.4) >5 yr 1.2 (0.6-2.6) >10 yr
[Muscat, et al. 2000]	66	0.8 (0.6-1.2)	28	1.1 (0.6-2.0) 2-3 yr	17	0.7 (0.4-1.49 ≥4 yr
[Inskip, et al. 2001]	139	0.8 (0.6-1.1)	51	1.0 (0.6-1.6) 0.5-3 yr	22	0.7 (0.4-1.4) ≥5 yr
[Johansen, et al. 2001]	154	1.0 (0.8-1.1)	87	1.1 (0.9-1.3) 1-4 yr	24	1.0 (0.7-1.6) >5 yr
[Auvinen, et al. 2002]	40 analogue 16 digital	1.3 (0.9-1.8)	15 analogue 11 digital	1.2 (0.7-2.0) 1-2 yr	18	1.5 (0.9-2.5) >2 yr
[Hardell, et al. 2002a]	188* analogue 224* digital	1.3 (1.0-1.6) 1.0 (0.8-1.2)	188* analogue 224* digital	1.3 (1.0-1.6) >1 yr 1.0 (0.8-1.2) >1 yr	46* analogue 33* digital	1.3 (0.8-2.3) >10 yr 0.9 (0.6-1.5) >5 yr
[Lönn, et al. 2005]	214 glioma 118 meningioma	0.8 (0.6-1.0) 0.7 (0.5-0.9)	112 64	0.8 (0.6-1.1) 1-4 yr 0.6 (0.4-0.9) 1-4 yr	25 12	0.9 (0.5-1.5) ≥10 yr 0.9 (0.4-1.9) ≥10 yr
[Christensen, et al. 2005]	47 low-grade glioma 59 high-grade glioma 67 meningioma	1.1 (0.6-2.0) 0.6 (0.4-0.9) 0.8 (0.5-1.3)	19 24 35	0.9 (0.4-1.8) 1-4 yr 0.6 (0.3-1.0) 1-4 yr 0.8 (0.5-1.3) 1-4 yr	6 8 6	1.6 (0.4-6.1) ≥10 yr 0.5 (0.2-1.3) ≥10 yr 1.0 (0.3-3.2) ≥10 yr
[Hardell, et al. 2005a; Hardell, et al. 2005c]	68 malignant, analogue 198 malignant, digital 35 meningioma, analogue 151 meningioma, digital	2.6 (1.5-4.3) 1.9 (1.3-2.7) 1.7 (1.0-3.0) 1.3 (0.9-1.9)	20 analogue 100 digital 1 analogue 96 digital	1.8 (0.9-3.5) 6-10 yr† 1.6 (1.1-2.4) 1-5 yr 1.2 (0.1-12) 1-5 yr 1.2 (0.8-1.8) 1-5 yr	48 analogue 19 digital 20 analogue 8 digital	3.5 (2.0-6.4) >10 yr 3.6 (1.7-7.5) >10 yr 2.1 (1.1-4.3) >10 yr 1.5 (0.6-3.9) >10 yr

* Discordant pairs

† No cases had shorter than 6 years latency

Table 2. Results for epidemiological mobile phone studies of acoustic neuroma:

	Acoustic neuroma		**Acoustic neuroma, short latency**		**Acoustic neuroma, longer latency**	
	No. exp cases	RR (95% CI)	No. exp cases	RR (95% CI)	No. exp cases	RR (95% CI)
[Hardell, et al. 1999]	5	0.8 (0.1-4.2)				
[Inskip, et al. 2001]	22	1.0 (0.5-1.9)	8	1.8 (0.7-4.5) 0.5-2 yr	5	1.9 (0.6-5.9)
[Johansen, et al. 2001]	7	0.6 (0.3-1.3)				
[Muscat, et al. 2002]			7	0.5 (0.2-1.3) 1-2 yr	11	1.7 (0.5-5.1) 3-6 yr
[Hardell, et al. 2002a]	38* analogue 23* digital	3.5 (1.8-6.8) 1.2 (0.7-2.2)	12* analogue 21* digital	3.0 (1.0-9.3) 1-5 yr 1.2 (0.6-2.2) 1-5 yr	7* analogue 2* digital	3.5 (0.7-16.8) >10 yr 2.0 (0.2-22.1) >5 yr
[Lönn, et al. 2004a]	89	1.0 (0.6-1.5)	44	0.8 (0.5-1.3) 1-4 yr	14	1.9 (0.9-4.1) ≥10 yr
[Christensen, et al. 2004]	45	0.9 (0.5-1.6)	23	0.9 (0.5-1.6) 1-4 yr	2	0.2 (0.0-1.1) ≥10 yr
[Hardell, et al. 2005a]	20 analogue 53 digital	4.2 (1.8-10) 2.0 (1.0-3.8)	2 analogue 29 digital	9.9 (1.4-69) 1-5 yr 1.7 (0.9-3.5) 1-5 yr	11 analogue 7 analogue 23 digital	5.1 (1.9-14) 5-10 yr 2.6 (0.9-8.0) >10 yr 2.7 (1.3-5.7) 5-10 yr
[Schoemaker, et al. 2005]†	360	0.9 (0.7-1.1)	174	0.8 (0.7-1.0) 1.5-4 yr	47	1.0 (0.7-1.5) ≥10 yr

* Discordant pairs

† Partly overlapping with Lönn et al, 2004 and Christensen et al, 2004