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Sixth annual report from SSM:s independent
Expert Group on Electromagnetic Fields 2009

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This report concerns a study which has been conducted for the Swedish Radiation Safety Authority, SSM. The conclusions and viewpoints presented in the report are those of the authors and do not necessarily coincide with those of the SSM.

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Preface

The Swedish Radiation Protection Authority, SSI (Statens strålskyddsinstitut) appointed an international independent expert group (IEG) for electromagnetic fields (EMF) and health in 2002. The Swedish government has reorganized the radiation protection work and the task of the IEG lie now under the newly formed Swedish Radiation Safety Authority (SSM). The task is to follow and evaluate the scientific development and to give advice to the SSM. 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. Because of the reorganization of the radiation protection work there was no annual report in 2008. The present report is thus the sixth in the series.

The composition of the group during the preparation of this report has been:

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Declarations of conflicts of interest are available at SSM.

Stockholm in December 2009

Anders Ahlbom

Chairman

Executive summary

A large number of cell studies are done on both genotoxic and non-genotoxic outcomes, such as apoptosis and gene expression. There are no new positive findings from cellular studies that have been well established in terms of experimental quality and replication. Potential heating of the samples is still seen as a major source of artefacts. Moreover, these few positive results are not related to each other and/or are not relevant for health risk assessment.

There are animal studies on brain structure and brain function as well as on genotoxicity and cancer. Also reproductive effects are looked at. However, animal studies have not identified any clear effects on any of a number of different biological endpoints following exposure to RF radiation typical of mobile phone use, generally at levels too low to induce significant heating.

Many human laboratory studies reviewed here are provocation studies with rather short exposures. Most use methods that are too crude, or look at phenomena that are too small, or non-existent, for the research to be informative. However, EEG alpha- and beta-frequencies seem to be sensitive to modulation by some pulse-modulation frequencies of the microwave- or GSM-signal. This curious effect does not have any behavioural counterpart, since similar types of EMF have been applied in various behavioural studies with negative results. This needs to be pursued. Surprisingly few studies have been done on children. In light of all official recommendations in different countries with special emphasis on children's use of mobile phones, this is rather peculiar.

Several epidemiological studies on mobile phone use and cancer have been presented since the previous report, including national studies from the Interphone group as well as other studies. There are also studies on reproductive outcomes. A few recent studies on people living near transmitters have also appeared. None of this changes any of the Groups previous conclusions. For conclusions, see the section on conclusions based on currently available data. However, one can draw some methodological conclusions at this point. One is that the problems in case control studies are too large for more such studies to be warranted at present. Another one is that cross-sectional research on symptoms, or other end points for that matter, also have too big inherent methodological problems to be warranted.

Conclusions on RF fields based on research available to date

Cancer and mobile phones

Overall the studies published to date do not demonstrate an increased risk of cancer related to mobile phone use within approximately ten years of use for any tumour of the brain or any other head tumour. Despite the methodological shortcomings and the limited data on long latency and long-term use, the available evidence does not suggest a causal association between mobile phone use and fast-growing tumours such as malignant glioma in adults (at least for tumours with short induction periods). For slow-growing tumours such as meningioma and acoustic neuroma, as well as for glioma among long-term users, the absence of association reported thus far is less conclusive because the observation period has been too short. This is consistent with results from animal and cellular research, which does not indicate that exposure of the type that is generated by mobile telephony, might be implicated in the origin or development of cancer. Long-term animal data on balance do not indicate any carcinogenic effect.

However, there are currently no data on mobile telephone use and cancer risk in children. For tumours other than intracranial, few epidemiological studies have been completed, but reasons to suspect an association with mobile telephony are even weaker than for tumours of the head.

Cancer and transmitters

The majority of studies on cancer among people who are exposed to RF from radio- or TV- transmitters or from mobile phone base stations have relied on too crude proxies for exposure to provide meaningful results. Indeed, only two studies, both on childhood leukaemia, have used models to assess individual exposure and both of those provide evidence against an association. One cannot conclusively exclude the possibility of an increased cancer risk in people exposed to RF from transmitters based on these results. However, these results in combination with the negative animal data and very low exposure from transmitters make it highly unlikely that living in the vicinity of a transmitter implicates an increased risk of cancer.

“Electromagnetic hypersensitivity, EHS”

While the symptoms experienced by patients with perceived electromagnetic hypersensitivity are very real and some subjects suffer severely, there is no evidence that RF exposure is a causal factor. In a number of experimental provocation studies, persons who consider themselves electrically hypersensitive and healthy volunteers have been exposed to either sham or real RF fields, but symptoms have not been more prevalent during RF exposure than during sham in any of the experimental groups. Several studies have indicated a placebo effect, i.e. an adverse effect caused by an expectation that something is harmful. Associations have been found between self-reported exposure and the outcomes, whereas no associations were seen with measured RF exposure.

Introduction

This year's report is biannual and, thus, covers a longer period than previous reports. The IEG's report of 2009 is focused on radio frequency fields, which includes electromagnetic fields used for mobile telecommunications. Recent research within this area includes *in vivo* and *in vitro* experimental research, studies based on human volunteers, and epidemiologic research. Because of the increasing importance of research on cognition, one of the vacancies on the IEG has been filled with an expert in that area and research on cognitive functioning and electromagnetic fields is reviewed in this report.

Preamble

In this preamble we explain the principles and methods that the IEG uses to achieve its goals.

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

A health risk assessment evaluates the evidence within each of these sectors and then weighs together the evidence across the sectors to a combined assessment. This combined assessment should address the question of whether or not a hazard exists i.e., if there exists a causal relation between exposure and some adverse health effect. The answer to this question is not necessarily a definitive yes or no, but may express the weight of evidence for the existence of a hazard. If such a hazard is judged to be present, the risk assessment should also address the magnitude of the effect and the shape of the dose-response function, i.e., the magnitude of the risk for various exposure levels and exposure patterns. A full risk assessment also includes exposure characterization in the population and estimates of the impact of exposure on burden of disease.

Epidemiological and experimental studies are subject to similar treatment in the evaluation process. As a general rule, only articles that are published, or accepted to be published, in English language peer-reviewed scientific journals are considered by the IEG. This does not imply that the IEG considers all published articles equally valid and relevant for health risk assessment. On the contrary, a main task of the IEG is to evaluate and assess these articles and the scientific weight that is to be given to each of them. The IEG examines all studies that are of potential relevance for its evaluations. However, in the first screening some of the studies are sorted out either because the scope is not relevant to the focus of a particular annual report, or because the scientific quality is insufficient to merit consideration. Such studies are normally not commented upon in the annual IEG reports. The IEG considers it to be of equal importance to evaluate positive and negative studies, i.e., studies indicating that EMF has an effect and studies not indicating the existence of such an effect. In the case of positive studies the evaluation focuses on alternatives to causation as explanation to the positive result: With what degree of certainty can one rule out the possibility that the observed positive result is produced by bias, e.g. confounding or selection bias, or chance. In the case of negative

studies one assesses the certainty with which it can be ruled out that the lack of an observed effect is the result of (masking) bias, e.g., because of too small exposure contrasts or too crude exposure measurements; one also has to evaluate the possibility that the lack of an observed effect is the result of chance, a possibility that is a particular problem in small studies with low statistical power. Obviously, the presence or absence of statistical significance is only a minor factor in this evaluation. Rather, the evaluation considers a number of characteristics of the study. Some of these characteristics are rather general, such as study size, assessment of participation rate, level of exposure, and quality of exposure assessment. Particularly important aspects are the observed strength of association and the internal consistency of the results including aspects such as dose response relation. Other characteristics are specific to the study in question and may involve dosimetry, method for assessment of biological or health endpoint, the relevance of any experimental biological model used etc. For a further discussion of aspects of study quality, refer for example to the Preamble to the IARC (International Agency for Research on Cancer) Monograph Series (IARC 2002). It is worth noting that the result of this process is not an assessment that a specific study is unequivocally negative or positive or whether it is accepted or rejected. Rather, the assessment will result in a weight that is given to the findings of a study.

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

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

An example demonstrating some of the difficulties of making an overall evaluation is the evaluation of ELF magnetic fields and their possible causal association with childhood leukaemia. It is widely agreed that while epidemiology consistently demonstrates an

association between ELF magnetic fields and increased occurrence of childhood leukaemia, the little support from observations in experimental models and the lack of support for plausible biophysical mechanisms of action leads to the overall evaluation of ELF magnetic fields, in IARC's terminology, as 'possibly carcinogenic to humans' (Group 2B).

Radiofrequency fields (RF)

Dosimetry

Exposure of children's heads to mobile phones

In the recent years several dosimetric studies have investigated the deposition of RF energy in the heads of children in comparison with those of adults. In the most recent published study, Wiart et al. (2008) reported that while the 10-g averaged SAR is not different between adults and children, there is a two-fold increase in maximum local SAR (averaged over 1 g) in brain peripheral tissues for children with ages ranging from 5 to 8 years. For older children the difference is no longer significant. According to the authors the main causes for this increase are the smaller thicknesses of pinna, skin and skull. This data are consistent with those published by Anderson (2003) and Wang & Fujiwara (2003). However, other studies were negative but did not always report the maximum local SAR (Keshvari & Lang 2005; Christ & Kuster 2005; Lee et al. 2007; Beard et al. 2006).

This has no direct influence on guidelines setting as the basic restriction is based on 10 g average, but it does show that the SAR at the periphery of the brain of young children is higher than in adults. In view of the current concern for children and the paucity of specific research devoted to this age range, it is a finding to bear in mind when designing and interpreting further research.

Whole-body dosimetry of children (or short people) exposed to far-field RF

There is now evidence that the ICNIRP reference levels are too high at certain frequencies to ensure that the basic restriction is not exceeded. This is based on the results of 13 studies which show that, under worst-case conditions, and around 2 GHz, the basic restriction is exceeded by a factor of approximately 40% for children younger than 8 years or people shorter than approximately 1.3 m (e.g., Wang et al., 2006; Dimbylow & Bolch 2007; Nagaoka et al., 2008; Conil et al., 2008; Findlay et al., 2009; Kühn et al., 2009). In 2009, ICNIRP has published a statement recognizing this fact (ICNIRP 2009). However, when the ICNIRP guidelines were set, the relationship between basic restriction and reference level was calculated using crude models. Therefore, ICNIRP states that the guidelines are still conservative as the reduction factor is 50 (i.e. 5000 %) while the discrepancy is around 50% at the maximum. Revision of the guidelines in the years to come will address this issue.

Cell studies

Cell-based assays are used extensively in toxicological investigations. This is because they can provide essential information about the potential effects of chemicals and other agents such as radiation on specific cell properties, and provide a more rapid and cost-effective approach to molecular and mechanistic studies than can conventional laboratory animal models. Studies *in vitro* have proved to be useful in elucidating mechanisms of action and are predictive for some health hazards and illnesses. However, when using simplistic cell-based systems to assess toxicity, it is important to recognize that cells are finely-balanced homeostatic machines that respond to external stimuli through complex pathways. As toxicity can be the result of a multitude of cellular events, and because cell culture systems often lack essential systemic contributors to overall absorption, distribution, metabolism and excretion, as well as to the complex interactions and effects of the immune, endocrine and nervous system, it is clear that no *in vitro* assays can completely mimic the *in situ* condition in animals and humans of complex interactions between stem cells, proliferating progenitor cells and terminally differentiated cells within a tissue and between tissues. *In vitro* investigations therefore only contribute to toxicity testing and risk assessment but, standing alone, they are insufficient predictors of toxicity and hazard.

The possibility that exposure to RF radiation affects DNA has, particularly since the introduction of wireless communication systems, been the subject of much debate. If it were shown that low-level exposure to RF electromagnetic fields induces genetic damage, this would certainly be indicative of a potentially serious public health risk. To date, the majority have been cytogenetic investigations of effects on the frequencies of chromosomal aberrations, sister chromatid exchanges and micronuclei, which can be used to identify potential cancer risk well before the clinical onset of disease. However, cytogenetic methods that reveal severe genetic damage are not able to detect most of the subtle indirect effects that may be induced. Improved methods or new technologies that may be more sensitive are therefore of great importance. These techniques include the comet assay, introduced some twenty years ago and the detection of γ -H2AX phosphorylated histone, one of the earliest marks of DNA double-strand breaks.

The assumption that genetic effects are exclusively and in all cases predictive for cancer is certainly an overstatement. It is now apparent that many chemicals can contribute to the carcinogenic process without inducing mutations. They may contribute to cancer by non-genotoxic or 'epigenetic' mechanisms rather than by mutation. Cellular responses depend on production of proteins (enzymes), key regulators of cell metabolic activity and behaviour. Protein structures are encoded in DNA (genes) and are produced by transcription of genes into mRNA and translation of the mRNA into protein. This activity is called gene expression and RF effects on gene expression are, more precisely, classified as either an effect on mRNA at the transcriptional level or on protein production. A large body of RF research has been conducted on gene and protein expression in mammalian and other cell types. The conventional method for analysis of gene expression is Northern blotting. More recently, reverse transcriptase polymerase chain reaction (RT-PCR) methods have been introduced. In its simplest form RT-PCR is not highly quantitative. However, several systems such as real-time RT-PCR have been

developed that allow highly precise quantification through the use of fluorescence measurements of specific gene products.

Conventional methods of protein analysis depend upon methods such as Western blotting and traditional biochemistry. In Western blotting, proteins are separated using acrylamide gels and transferred to membranes. The membranes are subsequently stained with antibodies to specific proteins of interest. The presence or absence of specific proteins and crude indications of relative abundance can be determined. Proteins can also be visualized in histological or cellular preparations using immunocytochemistry. Proteomics is the term applied to the global analysis of the protein complement of a cell. Typically, analysis is by two-dimensional (2D) gel electrophoresis, separating individual proteins on the basis of size and electric charge. These methods have been greatly improved in recent years by the development of standardised protocols and sophisticated image analysis software. Such automation provides the means for greatly increasing the amount of information that may be derived from a single experiment but at a cost, namely the increased difficulty in identifying biologically significant responses from experimental 'noise'.

With respect to *in vitro* investigations of RF radiation it should also be emphasized that the way RF exposure is done and hence proper dosimetry are crucial. Major improvements have been made in the quality of the exposure systems and their dosimetry. The average SAR value is a weak substitute for the real and rather complex exposure distribution in the Petri dishes or tissue culture vessels used. For a given exposure setup, cells can be exposed to SAR values that vary within a Petri dish. In addition, it is often difficult to specify temperature distribution accurately within the cell culture.

Genotoxic outcomes

DNA damage and reactive oxygen species (ROS)

There is still a continuous stream of experimental studies and reviews published on the genotoxic effects of RF exposure. This is due to some remaining uncertainty related to replication studies and to the interpretations of the various methods for assessing genotoxic effects.

In their review of the cell data Vijayalaxmi and Prihoda performed a meta-analysis to obtain a quantitative estimate of genotoxicity. They reviewed 63 publications (1990-2005) (Vijayalaxmi & Prihoda, 2008). Their analysis mainly dealt with single- and double-strand breaks in DNA, the incidence of chromosomal aberrations, micronuclei and sister chromatid exchanges, and monitored several key physical characteristics of the exposure. Their conclusion was that the size of the effect, when it occurred was small and under some specific exposure conditions there were some statistically significant increases in genotoxicity. However, the indices for chromosomal aberrations and micronuclei were within the levels reported in historical databases for all exposed and sham-exposed samples. Moreover, there was evidence for publication bias in terms of publishing weak positive effects (with often small sample size) more often than negative data (published only when the sample size was large).

The authors restated that no single genotoxic endpoint is capable of determining the genotoxic potential of the various agents. This is an excellent and much needed review of the papers on genotoxicity and RF. The conclusion is that the effects are weak or inconclusive. This review does not include the papers below.

The Rüdiger group at the University of Vienna has published new findings on genotoxic effects that occur in human fibroblasts but not in lymphocytes, exposed to UMTS signals (Schwarz et al., 2008). The cells were exposed at 1950 MHz at up to 2 W/kg. The alkaline comet assay and the micronucleus assay were used to assess the potential genotoxic effects. In human cultured fibroblasts, UMTS exposure increased counts in both assays in a dose and time-dependent way, but not in lymphocytes. As the effect was obtained even at the low SAR level of 0.05 W/kg, the authors speculate that an indirect mode of genotoxic action is occurring, i.e., an epigenetic process.

This paper was criticized by Lerchl (2009) based on a statistical analysis of the data of Swartz et al. (2008) showing a very small coefficient of variation in the comet data and inter-individual differences of the data in strong disagreement with previously published data. The author expressed his concern about the origin of the reported data. This paper came before an accusation of fraud was made concerning both Vienna publications (see Vogel, 2008).

In his published answer, Rüdiger (2009) refuted the Lerchl comments by arguing that low coefficients of variation were consistently found by his group using visual classification of the comets, which has been criticized by other authors as not being objective.

In China, Yao et al. (2008) investigated the effects of the addition of electromagnetic noise on DNA damage and intracellular ROS concentration increase in cultured human lens epithelial cells induced by exposure to GSM 1800 signals. The two-hour exposures were done at 1, 2, 3, and 4 W/kg. ROS levels were assayed using the fluorescent probe DCFH2¹ (see comment below on the use of the DCFH2 probe) and DNA damage using the alkaline comet assay. ROS and comet increases were seen above 2 W/kg and above 3 W/kg, respectively. When noise (2 μ T, 30–90 Hz white noise) was added these effects disappeared. The conclusion of the authors is that increased ROS production, which would be the cause of DNA damage, is blocked by electromagnetic noise.

In still another study on DNA damage and ROS, Luukkonen et al. (2009) in Finland exposed SH-SY5Y neuroblastoma cells to GSM 900 signals at 5 W/kg for 1 hour, alone or in combination with menadione which induces intracellular ROS production and DNA damage. Again, ROS production was measured using the fluorescent probe DCFH-DA and DNA damage using the Comet assay. Exposure to continuous-wave (CW) RFR increased DNA breakage in comparison to cells exposed to menadione alone. ROS level was higher in cells exposed to CW RFR at 30 and 60 min after the end of exposure. No effects of the GSM signal were seen on either end point. The occurrence of effects caused by CW exposure and not GSM RF at an identical SAR is highly surprising as the opposite is more likely in view of the peak power of GSM which is 8 times above CW. Moreover, at 5 W/kg in the exposure system used in this work, heating of the cells cannot be excluded (see comment below on temperature control).

¹ dichlorodihydrofluorescein

The same group (Höytö et al., 2008a) used the same physical and biological protocols on human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells and induced lipid peroxidation using tert-butylhydroperoxide (t-BOOH). After 1 or 24 h of exposure, cellular glutathione (GSH) levels, lipid peroxidation, proliferation, caspase 3 activity, DNA fragmentation and viability were assessed. Lipid peroxidation induced by t-BOOH was increased in SH-SY5Y (but not in L929) cells, and menadione-induced caspase 3 activity was increased in L929 but not in SH-SY5Y cells, and only for the GSM signal. No effects were observed from exposure to RFR alone. According to the authors, the results do not support induction or enhancement of oxidative stress under exposure, as cellular GSH levels were not affected. Proliferation and cell viability were not affected under any of the experimental conditions. RFR alone, without stress-inducing chemical agents, had no effects on any of the end points measured.

A Korean CDMA signal was used by Kim et al. (2008) to test the effects on mammalian cells alone and in combination with clastogens. In the comet assay and chromosome aberration test, there was no effect of exposure alone (4 W/kg). However, in combination with cyclophosphamide or 4-nitroquinoline 1-oxide, RF exposure had a potentiating effect. Heating of the cells cannot be excluded, as no dosimetric analysis was given and there was no fan or other cooling system in spite of the high SAR level.

Genomic instability was investigated by Mazor et al. (2008) in Israel, on lymphocytes exposed in a waveguide at 2.9 and 4.1 W/kg (CW, 800 MHz, 72 hours). The induced aneuploidy (abnormal copy number of genomic elements) was determined by interphase FISH² using a semi-automated image analysis method. Increased levels of aneuploidy were observed depending on the chromosome studied as well as SAR exposure. According to the authors, the findings provide some evidence of non-thermal effects of RF radiation that causes increased levels of aneuploidy.

The effect of “pre-exposure” to RF was tested by the group of Scarfi in Italy (Sannino et al., 2009a) in peripheral blood lymphocytes using the micronucleus test. After stimulation with PHA³ for 24 h, cells were exposed to a GSM 900 signal at 10 W/kg for 20 h and then challenged with a single genotoxic dose of mitomycin C at 48 h. Lymphocytes were collected at 72 h to examine the frequency of micronuclei in cytokinesis-blocked binucleated cells. Lymphocytes that were pre-exposed to 900 MHz RF had a significantly decreased incidence of micronuclei induced by the challenge dose of mitomycin C. These preliminary results suggested that an adaptive response can be induced in cells exposed to non-ionizing radiation.

The same group (Sannino et al., 2009b) investigated DNA damage in human dermal fibroblasts from a healthy subject and from a subject affected by Turner’s syndrome. The cells were exposed for 24 h to GSM 900 at 1 W/kg. RF exposure was carried out alone or in combination with MX (3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone, 25 mM for 1 h immediately after the RF exposure). The alkaline comet assay and the cytokinesis-block micronucleus assay were used. No genotoxic or cytotoxic effects were found from

² fluorescence in situ hybridization: cytogenetic technique used to detect and localize the presence or absence of specific DNA sequences on chromosomes.

³ phytohemagglutinin

RF exposure alone in either cell line. As expected, the MX treatment induced an increase in DNA damage, but there was no enhancement of the MX-induced DNA damage in the cells exposed to RF, nor differences between cells from normal and Turner's syndrome patients.

Comment on the use of the DCFH2 probe for assessing ROS effects:

Several groups have investigated the potential effects of RF exposure on ROS formation or concentration. As described above, some of them are using the fluorescent probe DCFH2 which is oxidised by ROS to the fluorescent species DCF⁴. Recently, Wardman (2008) has warned about (i) the proper use of the term ROS which is a crude and increasingly inadequate descriptor of over 20 species, both radical and non-radical entities, and many not oxygen-centred and (ii) the lack of discussion as to which ROS are being measured, which must reflect the reactivity of individual ROS toward the probe, and the chemical mechanisms involved in transformation of the DCFH2 probe to the measured DCF.

Comment on temperature control in cellular experiment:

In spite of all efforts made to keep the temperature of the cells under exposure at nominal temperature, several key results have shown that above around 2 W/kg, bioeffects due to subtle temperature gradients or differentials cannot be excluded.

Comment on statistical power:

In several of the studies with low sample numbers, the statistical power is such that negative results cannot be established with confidence. This is not often discussed by the authors.

Non-genotoxic outcomes

Endocytosis

The French group of Mir had shown that fluid phase endocytosis rate increased in cells exposed to GSM 900 and to electric pulses similar to the GSM electrical component (Mahrouf et al. 2005). In this new study (Moisescu et al., 2009), murine melanoma cells were exposed to Lucifer Yellow (LY) and to GSM-EMF/electric pulses in the presence of drugs inhibiting the clathrin- or the caveolin-dependent endocytosis (3.2 W/kg, 28.5-29.5 °C). There was an increase in LY uptake under exposure that cannot be caused by temperature elevation as established in control experiments done as a function of temperature. Chlorpromazine and ethanol, but not Filipin, inhibited this increase. This suggests that the cellular mechanism involves vesicles that detach from the cell membrane, mainly clathrin-coated vesicles. The authors did not conclude about the relevance of their findings for health effects.

Apoptosis

The current consensus about apoptosis is that it is not induced by RF exposure of cells. This conclusion was challenged by the findings of a French group (Joubert et al., 2008). The authors exposed rat primary neuronal cultures for 24 h to CW 900 MHz RF at 2 W/kg, which caused a 2°C temperature elevation of the medium. Control experiments

⁴ dichlorofluorescein

with neurons exposed to 39 °C were thus performed. Apoptosis was assessed by standard method including TUNEL⁵. Under the experimental conditions used, exposure of the neurons to CW RF fields induced a caspase-independent pathway to apoptosis that involves the apoptosis-inducing factor (AIF). However, there is a potential bias in the experiment since the temperature was allowed to rise under exposure. Under these conditions, even with a control sample set at the same temperature, there is a risk of modifying the cell biochemistry at temperatures away from the nominal level, thereby affecting the outcome of the assay.

Transformation

There is currently a lack of studies on the potential effects of RF exposure on cell neoplastic transformation.

The Japanese group of Miyakoshi investigated the effects of exposure of BALB/3T3 cells, which are the cells most often used in this type of transformation assay, to 2.14 GHz W-CDMA RF fields at 0.08 and 0.8 W/kg for 6 weeks (Hirose et al., 2008). In addition, MCA⁶-treated cells were RF exposed, to assess for effects on tumour promotion. Moreover, the effect of RF exposure on tumour co-promotion was assessed in the cells initiated with MCA and co-exposed to the tumour promoter TPA⁷. There were no effects of RF exposure under any of the conditions. The only weakness of this study is the relatively low SAR level used.

Gene expression

In their recent review on genome-wide and/or proteome-wide response after exposure to RF, Vanderstraeten & Verschaeve (2008) analysed all papers reported using high-throughput screening techniques (HTSTs). According to the authors, these studies are still inconclusive, as most of the positive findings are flawed by methodological imperfections or shortcomings. Their conclusion is that the role of transcriptomics and proteomics in the screening of RF bioeffects is still uncertain in view of the lack of positively identified phenotypic change and the lack of theoretical, as well as experimental, arguments for alteration of gene and/or protein response patterns.

This view is not shared by several scientists who claim that HTSTs are needed to remove the uncertainty that remains on bioeffects of non-thermal RF. However, most of the recent publications report negative effects on gene expression, such as the two papers below:

In Italy, Valbonesi et al. (2008) exposed human trophoblast cell line HTR-8/SVneo to GSM 1800 at 2 W/kg for 1 hour and evaluated the expression of proteins (HSP70 and HSC70) and genes (hsp70A, B, C and hsc70). Positive controls were used successfully. There was no change in gene or protein expression under these exposure conditions.

Reports that low-intensity microwave radiation induces heat-shock reporter gene expression in the *Caenorhabditis elegans* nematode had been reinterpreted as a subtle thermal effect caused by a slight heating. The same group in the UK (Dawe et al., 2009)

⁵ Terminal deoxynucleotidyl transferase dUTP nick end labeling

⁶ 3-methylcholanthrene

⁷ 12-O-tetradecanoylphorbol-13-acetate

extended their investigations using the same biological model and an exposure system that minimises temperature elevation (1.0 GHz, 0.9–3 mW/kg). Five Affymetrix gene arrays of pooled triplicate RNA were used for each exposed and sham-exposed samples. No genes showed consistent expression changes across all 5 comparisons. A weakness of this study, in terms of extrapolation, is the use of a very low SAR level.

In a very recent review by McNamee and Chauhan (2009), the conclusion of the authors was that *“when taken collectively, the weight of evidence does not support the notion of specific, non-thermal responses to RF radiation at the gene or protein level. Nevertheless, a few well-conducted studies have observed sufficient evidence of possible RF-radiation-induced gene/protein interaction to warrant further investigation.”*

Calcium

Following initial reports of effects of ELF-modulated RF exposure on the calcium ion in cells and brain tissue, few new studies have been published on the topic in the last ten years. However, one group in the USA (Rao et al., 2008) recently reported alteration of $[Ca^{2+}]_i$ dynamics. Exposure was done from 700 to 1100 MHz at 0.5-5 W/kg (Pickard et al., 2006). Neuronal cells differentiated from a mouse embryonic stem cell line were used and the cytosolic $[Ca^{2+}]_i$ monitored. The observed increase in the calcium spiking was dependent on frequency but not on SAR. N-type calcium channels and phospholipase C enzymes appeared to be involved in mediating the increased spiking.

These findings are at odds with previous reports and the observation of a dependence on carrier frequency (maximum effects at 800 MHz) is puzzling, and may be a hint that artefacts are produced in the exposure system. This explanation was suggested by the authors themselves.

Ornithine decarboxylase (ODC)

Following the reports by the Litovitz group in the USA of increases in ornithine decarboxylase (ODC) activity in cells exposed to RF signals (Penafiel et al., 1997), a two-laboratory investigation was launched and its results are now available.

In Finland, Höytö et al. (2009b) exposed murine L929 fibroblasts stimulated with fresh medium, stressed with serum deprivation or not subjected to stimulation or stress, in a waveguide exposure system to 872 MHz CW or GSM RFR at 5 W/kg. ODC activity was assessed after 1- and 24-h exposures, proliferation during 48 h after 24 h exposure, and caspase-3 activity after 1 h exposure. No consistent effects of RF exposure were found. Moreover, stressed and stimulated cells were not more sensitive than normal cells.

In France, Billaudel et al., (2009a) also used murine L929 fibroblasts and exposed them in various systems to DAMPS and GSM signals. In a TEM cell with the DAMPS signal at 835 MHz and 2.5 W/kg, there was no alteration in ODC activity after one-hour exposure. This was true also with GSM 900 and 1800 signals.

In a subsequent paper of the same group (Billaudel et al., 2009b) the study was extended to human neuroblastoma cells (SH-SY5Y) which was deemed more relevant than the fibroblast model. Cells were exposed to 50 Hz-modulated DAMPS-835 or GSM-1800 for 8 or 24 hours using waveguides equipped with fans. There was no alteration of ODC activity under any exposure condition.

In conclusion of this collaborative project, the findings of the Litovitz group on ODC activity could not be confirmed.

Microglial cells

In Japan, the effects of RF exposure were tested on the immune component of the brain; the microglial cells (Hirose et al., 2009). Changes in immune reaction-related molecule expression and cytokine production were monitored in primary microglial cell cultures prepared from neonatal rats. A 3G signal at 1950 MHz was used at 0.2, 0.8, and 2.0 W/kg. There was no difference in the amount of cells positive for the major histocompatibility complex (MHC) class II, a common marker for activated microglial cells, nor were the levels of tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) altered by exposure.

This report of an absence of effects of RF exposure *in vitro* on microglial cells is consistent with a few recently published studies (e.g., Thorlin et al., 2006).

Neurodegenerative models

In Italy, Del Vecchio et al. (2009) exposed neural cells to GSM 900 at 1 W/kg to model neurodegenerative processes. They tested the viability, proliferation, and vulnerability of the cells (SN56 cholinergic cell line and rat primary cortical neurons) under exposure and in the presence of neurotoxic molecules, (glutamate, 25-35AA beta-amyloid, and hydrogen peroxide). RF exposure alone did not alter the cells parameters but the neurotoxic effect of hydrogen peroxide was increased by RF exposure in SN56 but not in primary cortical neurons. These results give some evidence that combined exposure to RF and some neurotoxic agents might alter oxidative stress in cells.

Fertility

There is currently a concern about possible effects of mobile phone exposure on male fertility. Some investigations have been done *in vitro* to address that concern. De Iuliis et al. (2009) have used purified human spermatozoa exposed to GSM 1800 signals at SAR ranging from 0.4 to 27.5 W/kg. Motility and vitality of the spermatozoa were significantly reduced after exposure, with increasing SAR level, while the mitochondrial generation of ROS and DNA damage were significantly elevated. Several methods were used to quantify ROS and DNA damage but the design of the exposure system and its dosimetry were not done using to the most modern techniques available, and heating of the cells at high SAR cannot be excluded. However, replication of these findings is warranted.

Conclusions on cellular studies

There are no new positive findings from cellular studies that have been well established in terms of experimental quality and replication. Potential heating of the samples is still seen as a major source of artefacts. Moreover, these few positive results are not related to each other and/or are not relevant for health risk assessment. It is warranted that further *in vitro* studies that are well designed will help fill the remaining gaps such as effects on transformation.

Animal studies

Animal studies are frequently based on experiments using laboratory strains of mice or rats. The advantage of such studies is that they provide information concerning the interaction of RFR with living systems, which display the full repertoire of body functions, such as immune response, cardiovascular changes, and behaviour, in a way that cannot be achieved with cellular studies. Transgenic or gene knockout animal models of certain diseases have further increased the value of animal studies to reveal potential adverse health effects. Animal studies are thus usually a more powerful experimental tool than cellular studies in this context. However, extrapolation to humans is not straightforward, since there are obvious differences in physiology and metabolism between species, as well as differences in life expectancy and many other variables. Nevertheless, at a molecular level, there are many similarities between processes in animals and humans and such studies have been very useful in helping unravel the sequence of genetic events in the development of a number of human cancers.

Generally, animal studies can be expected to provide qualitative information regarding potential outcomes, but the data cannot be extrapolated quantitatively to give reliable estimates of human risk for the reasons outlined above. In addition, differences in body size, which are particularly marked in laboratory rodents compared to humans, means that dosimetric interaction is different, small animals showing body resonance to RF radiation at higher frequencies than humans, with a comparatively greater depth of penetration relative to body size. The selection of RF exposure systems used in animal studies is often a compromise between restraint-related stress and the accuracy of RF dosimetry. Immobilization of animals has been used in many animal studies to achieve well-defined dosimetry but this can cause restraint-related stress that might affect the outcome of the experiment unless appropriate steps, such as the habituation of animals to restraint, are taken. In addition to blind scoring, where the exposure status of the sample is unknown to the scorer in order to eliminate subjective bias, some of the studies also use positive controls, where an agent is used which is known to induce the effect or lesion being studied so as to ensure that the experimental protocol has the necessary detection sensitivity.

Studies of the effects of RF exposure on animals over the past two years have focussed mostly on the brain using high throughput screening techniques to study RF effects on gene expression but also looking at more general biochemical, histopathological and behavioural changes. Otherwise, a few studies have examined genotoxic, carcinogenic, reproductive, developmental, auditory, endocrine and immunological effects.

Brain and behaviour

The effects of RF on the brain and behaviour have been reviewed by a number of authors (e.g. D'Andrea et al, 2003a, 2003b; Sienkiewicz et al, 2005). The IEG concluded in its last report (IEGEMF, 2007) that while many studies find no evidence of RF effects on the nervous system, a few studies have reported changes in behavioural tests, electrical (EEG) activity and neurotransmitter metabolism. Generally, however, the only consistent changes reported are those associated with heating or restraint stress.

Gene expression

Several studies carried out in the 1990's of the effects of RF exposure on gene expression in the brains of laboratory rodents were variable and generally negative (IEGMP, 2000). Most examined effects on individual genes such as *fos* and *jun* that respond to various stressors. Generally, increased expression was seen only following thermally significant exposures. More recent analyses have tended to use oligonucleotide chips or cDNA glass microarrays to make quantitative measures of gene expression of large numbers of genes from exposed and unexposed cell populations. Interpretation of the results however relies heavily on complex statistical analysis that is very sensitive to the applied level of stringency with which meaningful responses are identified (see IEGEMF, 2006). In addition, it is widely acknowledged that there is a need to verify any ensuing changes in individual gene expression through other techniques such as real-time RT-PCR.

Paparini et al (2008) carried out microarray analyses of 22,600 genes in the whole brain tissue of a total of 30 mice (15 per group) exposed or sham-exposed to GSM-1800 MHz signals at a brain SAR of ~ 0.2 W/kg for 1 h. In contrast to the study by Nittby et al (2008a) described below, gene expression in the brain tissue of exposed mice was not significantly different from the brain tissue of mice sham-exposed. In this analysis, the fold change in expression required for scoring as an upregulation or downregulation of gene expression was 1.5 or 2.0. Applying other less stringent constraints revealed that 75 genes modulated their expression between 0.67 to 2.8 fold, including several gene ontology functions such as transcription regulation and transporter activity. However, real-time RT-PCR analysis did not confirm the observed changes in expression.

Nittby et al (2008a) carried out microarray analyses of 31,099 genes from hippocampal and cortical tissue of the brains of a total of 8 rats (4 per group) following exposure or sham-exposure to GSM-1800 MHz signals at an average whole body SAR of 13 mW/kg (brain SAR of 30 mW/kg) for 6 h. Using gene ontology analysis to examine the expression of various functional categories of genes (signal transducer activity, voltage-gated ion channel activity etc), the authors reported significantly altered expression in some categories of gene in both cortex and hippocampus of the exposed rats compared to those from sham-exposed controls. Four of the 10 most significantly altered categories were associated with membrane receptor function. However, the number of animals per group was very low and fold change in expression required for scoring as an upregulation or downregulation of gene expression category was unusually small (0.05). The authors noted that RF exposure did not significantly alter the expression of individual genes.

Yan et al (2008) investigated the effect of prolonged exposure of adult rats to RFR on changes in rat brain tissue of mRNA levels of several injury-associated proteins (Ca^{2+} -ATPase, *ncam-1*, *ngf-b*, and *vegf-a*) necessary for cellular repair. Adult Sprague-Dawley rats (variously described as 7 or 8 per group) were exposed or sham-exposed to RFR from four (Nokia 3588i) mobile phones which operate at both 800 and 1900 MHz. Each phone was situated 1 cm away from the heads of two rats held either side of the phone in PVC tubes. SARs at 2.2 cm distance from the phone, presumably representing the SAR in a part of the brain, were briefly described as somewhere between 0.00001 and 1.8 W/kg, depending on the mode in which the phones were operating (not given). The exposures were carried out 6 h per day for 18 weeks. RT-PCR analysis revealed that the RF-exposed animals had significantly elevated mRNA levels of all four injury-associated

proteins. However, these results can only be considered as preliminary: the exposure and dosimetry procedures were questionable and simple RT-PCR analysis is less quantitative than other currently available techniques.

Metabolic responses, glial cell injury, cell proliferation and apoptosis

Heat shock proteins (HSPs) are involved in cellular stress responses and their induction by RFR has been examined in a number of *in vitro* and animal studies. IEGEMF (2003) concluded that effects on the expression of HSPs at levels below the thermal threshold, estimated at around 7 W/kg *in vivo*, had not been confirmed. More recently, Finnie et al (2009) examined the effects of GSM-900 MHz signals throughout gestation on HSP expression in the fetal mouse brain. Pregnant mice were exposed or sham-exposed (10 per group) to GSM-900 MHz signals at a whole-body SAR of 4 W/kg for 1 h per day every day from day 1 to day 19 of gestation. Following exposure, the animals were sacrificed and one fetal brain was selected from each litter for neuropathological examination. Three coronal brain sections were taken encompassing wide range of anatomical regions of the brain and immunostained for HSP25, HSP32 and HSP70. The authors found no evidence of the induction of HSP32 or HSP70 in the mouse brain, and noted that HSP25 expression was limited to two brainstem regions in both exposed and sham-exposed animals.

Ammari et al (2008a) assessed the effect of exposure to GSM signals on rat brain metabolic activity by measuring cytochrome oxidase levels in brain tissue. Cytochrome oxidase is a specific marker of oxidative metabolism in the brain, and reflects neuronal activity over prolonged periods. Twenty four rats (6 per group) were exposed or sham-exposed to GSM 900 MHz signals at a brain-averaged SAR of 1.5 W/kg for 15 min per day or at 6 W/kg for 45 min per day for 7 days; the fourth group acted as cage controls. Animals were sacrificed 7 days following the cessation of exposure. Compared to the sham-exposed group, significant decreases were found in cytochrome oxidase activity in areas close to the RF antenna (the prefrontal and frontal cortex) and in deeper structures (the posterior cortex, the hippocampus and septum) of animals exposed at 6 W/kg but not in those exposed at 1.5 W/kg, again raising the possibility that the effects were thermal in nature.

Sokolovic et al (2008) studied the effect of prolonged exposure to GSM 900 MHz signals phone radiation on oxidative stress in the rat brain and the amelioration of this effect by melatonin. The authors exposed or sham-exposed 84 rats (12 groups of 7 rats) for up to 60 days from Nokia 3110 mobile phones or sham phones placed within the centre of each cage for 4 hr per day at an estimated whole-body SAR of between 0.043 and 0.135 W/kg. Rats from half of the sham-exposed and exposed groups were treated with daily intraperitoneal injections of melatonin (2 mg/kg). The rats were sacrificed 20, 40 or 60 days after exposure and brain tissue examined for the degree of lipid and protein oxidation, and the activity of the anti-oxidants catalase and xanthine oxidase. The authors found that RF radiation significantly enhanced lipid and protein oxidation and significantly reduced catalase and xanthine oxidase activity after exposure. Melatonin treatment prevented the enhancement of lipid oxidation and the reduction in xanthine oxidase activity after exposure. The authors conclude that GSM radiation resulted in oxidative damage to brain tissue and that this can be partially prevented by melatonin

treatment. However, the dosimetry was highly uncertain since the rats were free to move around the mobile phone source, and therefore the RF radiation absorbed by the brain of each exposed rat must have been variable. This raises questions about the significance of these results.

Two groups have examined the effects of mobile phone type RF radiation on glial fibrillary acidic protein (GFAP) expression, taken as an indicator of glial cell response to injury. Early studies by De Seze and colleagues have reported changes induced in GFAP expression in the rat brain following exposure to GSM-900 MHz fields. However, the IEGMP (2007) concluded that local temperature changes remain a possible explanation and that the relevance of these studies to human risk assessment is unknown at present. More recently, the same group (Ammari et al, 2008b) examined the effect of a chronic exposure to GSM-900 MHz signals on GFAP expression in the rat brain. In this experiment, 24 rats (6 per group) were exposed or sham-exposed to GSM-900 MHz signals at a brain-averaged SAR of 1.5 W/kg for 15 min per day or 6 W/kg for 45 min per day, 5 days per week for 24 weeks. A fourth group acted as cage controls. Animals were sacrificed 10 days following the cessation of exposure. Immunocytochemical techniques were used to determine GFAP expression in brain tissue. Compared to the sham-exposed group, significant increases in the percentage staining of GFAP expression but not in optical density were found in the prefrontal cortex, the dentate gyrus, the caudate putamen and the lateral globus pallidus of animals exposed at 6 W/kg but not in those exposed at 1.5 W/kg, raising the possibility that the effect was thermal in nature.

In contrast, glial cell injury, cell proliferation and apoptosis were unaffected by the exposure of mice for up to 12 months to RFR from Korean mobile phones (Kim et al, 2008); 120 mice were subdivided into groups of 40 (20 male and 20 female) and their heads exposed to 849 or 1763 MHz (CDMA) RFR at a SAR of 7.8 W/kg or sham exposed for 1 h per day, 5 days per week. The mice were sacrificed after 26 or 52 weeks of exposure, and immunohistochemical techniques were used to examine effects on GFAP expression, cell proliferation and apoptosis in tissues of the hippocampus and cerebellum.

Blood-brain barrier histopathology

Early studies on the potential effects of mobile telephony signals on the permeability of the blood-brain barrier, which prevents the movement of toxins into the brain, have been previously discussed (IEGEMF, 2003). In particular, a number of positive studies mostly by Salford and colleagues at Lund University in Sweden described an increase in permeability of the blood-brain barrier and the number of dark neurons, taken by these authors to indicate neuronal damage, at various times between 1 h and 50 days following exposure to low level GSM radiation (e.g. Salford et al, 1994, 2003; Persson et al, 1997). Salford et al (2003), for example, reported that exposure of male and female rats of various ages to pulsed 915 MHz radiation for 2 h at SARs between 2 and 200 mW/kg caused increased blood-brain barrier permeability to albumin and an increased number of darkly staining neurons, especially in the cortex, hippocampus, and basal ganglia, 50 days following exposure. IEGEMF (2003) described various technical weaknesses in the paper, including poor dosimetry and inappropriate staining techniques, noting that most studies from other laboratories reported no effect. They concluded that a careful analysis

of the available data did not indicate the presence of a health risk but further work need to be carried out. Some more recent studies including attempted corroborations of earlier studies are discussed below.

Salford and colleagues subsequently carried out a number of studies further exploring the effects alluded to above. In one study, Eberhardt et al (2008) investigated the effect of acute exposure to GSM-900 MHz radiation on the permeability of the blood-brain barrier and neuronal damage in the rat brain. Ninety six rats (8 animals per group) were exposed or sham exposed for 2 h at whole-body SARs between 0.12 and 120 mW/kg and sacrificed 14 or 28 days after exposure. Brain tissue was examined for extravasation of the protein albumin, taken as a measure of the integrity of the blood-brain barrier, and for the occurrence of darkly staining neurons. A significant increase in extravasation of albumin was seen 14 days after exposure in some exposed groups but not 28 days after exposure whereas dark neurons were significantly increased 28 days but not 14 days after exposure. These effects, which showed no obvious dose-response relationship, were most marked in the cortex, hippocampus and basal ganglia. In a follow-up study, Nittby et al (2009a) examined the effects of the same exposure given above in 48 rats (8 rats per group) sacrificed 7 days after exposure. In contrast to the results seen above, albumin extravasation was greatest in animals exposed at 12 mW/kg. No effects on the incidence dark neurons were described.

Further studies by Salford and colleagues (Grafström et al, 2008) investigated possible effects on the brains of the 56 rats used by Nittby et al (2008b – see below) in their study of the possible effects of prolonged GSM radiation on the performance of a recognition memory task. As described below, 32 rats were exposed to 915 MHz GSM-type mobile phone radiation at whole-body SARs of 0.6 and 60 mW/kg for 2 h per week for 55 weeks. A further 16 rats were sham-exposed and 8 acted as cage-controls. The rats were sacrificed 5-7 weeks after the last RF exposure and examined for the presence of albumin extravasation and for the presence of dark neurons. However, no statistically significant differences were found between the exposed and sham-exposed groups in any parameter, nor was there any effect of SAR. The authors note that the permeability changes and occurrence of dark neurons seen in earlier studies of the acute effects of short-term exposure were not seen in this long-term study.

Three groups have published the results of studies which attempted to corroborate some of the work of Salford and colleagues using the same rat strain, but avoiding some of the weaknesses in the original studies such as the use of rats of widely differing ages. McQuade et al (2009) carried out a study designed to confirm whether exposure to 915 MHz radiation, using a similar transverse electromagnetic transmission line (TEM) exposure cell and similar exposure parameters to those used by Salford and colleagues, caused the extravasation of albumin in rat brain tissue. These authors exposed or sham exposed the rats (28-46 per group) for 30 min to CW 915 MHz or 915 MHz radiation pulse-modulated at 16 or 270 Hz at whole-body SARs ranging between 1.8 mW/kg and 20 W/kg and examined the brain tissue shortly after exposure. The authors examined coronal sections from three or more regions along the rostral-caudal axis, assigning scores for extracellular extravasation across the whole section. Separate brain regions in each section were distinguished but these results were not presented. Overall, McQuade et al (2009) reported little or no extracellular extravasation of albumin in the brain tissue of

any exposure group compared to sham exposed animals, in contrast to the effects seen in the positive control groups.

Masuda et al (2009) attempted a more direct confirmation of work by Salford and colleagues. These authors examined the effects on 82 rats (5 groups of 16 rats) of a single 2 h exposure or sham exposure to GSM-915 MHz radiation in a similar TEM cell at whole body SARs of between 20 mW/kg and 2.0 W/kg, following and extending the experimental protocol used by the Lund group. The effects on the extravasation of serum albumin and on the appearance of dark neurons were evaluated histologically 14 or 50 days after exposure. The authors reported that they were unable to find any evidence of increased albumin extravasation or dark neurons in the brain tissue of exposed animals, although clear increases in both were seen in the positive control groups. In their discussion, Masuda et al (2009) noted that in addition to the staining techniques for both endpoints used by the Lund group they also used improved techniques that were less susceptible to artefacts.

Poullietier de Gannes et al (2009a) also used improved staining techniques, as well as those originally used by the Lund group, in order to identify albumin extravasation and the presence of dark neurons in rat brains 14 or 50 days after the head-only exposure or sham exposure of rats (8 rats per group) for 2 h to a GSM-900 signal at brain averaged SARs of 140 mW/kg and 2.0 W/kg. In addition, Poullietier de Gannes and colleagues used a more specific marker for neuronal degeneration than the one used by the Lund group and also looked for the presence of apoptotic neurons. Like McQuade et al (2009) and Masuda et al (2009), Poullietier de Gannes et al (2009a) also used a cage-control group and a positive control group. The authors reported that they were unable to find any evidence of increased albumin extravasation, neuronal degeneration, dark neurons or apoptosis in 12 different regions of rat brain tissue of exposed animals, although clear increases in both were seen in the positive control group.

Thus, the observations of Salford and colleagues have not been successfully confirmed by these three groups, although there were various differences in experimental protocol partly to avoid some of the technical weaknesses in the original studies. These improved methodologies included the use of larger numbers of single sex (male) rats of a narrower age range, habituation of the rats to the exposure system and improved fixation and staining methods. Overall, the lack of corroboration by these different laboratories and absence of any coherent dose-response relationship considerably weakens confidence in the original observations.

Behaviour

A number of studies have examined RF effects on the performance of spatial memory tasks. Initial studies by Lai and colleagues suggesting large field-dependent deficits in task performance by rats exposed to low level pulsed 2.45 GHz fields have not been confirmed by a number of other laboratories (reviewed by Sienkiewicz et al, 2005). However, one recent study has reported an impaired performance of an object recognition task following prolonged chronic exposure to mobile-phone type radiation. Previously, the performance of an object-recognition task had been impaired following acute exposure to 600 MHz RF radiation only at hyperthermal levels (Mickley et al, 1994).

Nittby et al (2008b) investigated the effects of exposure of 32 rats to GSM- 915 MHz radiation at whole-body SARs of 0.6 and 60 mW/kg for 2 h/week for 55 weeks on open-field behaviour, which examines anxiety levels and exploratory behaviour in an open arena, and the performance of a place and object-recognition task, which tests long-term “episodic-like” memory for objects, their spatial location and order of presentation. Sixteen rats were sham-exposed and 8 acted as cage-controls. Exposures were coded so that the behavioural testing was carried out ‘blind’. The behavioural tests were carried out between 3-7 weeks after RF exposure. The authors found that RF exposure had no effect on general locomotor or exploratory activity or on anxiety. Normally, in this task, rats spend less time exploring a recently presented object than an object that has been presented earlier, and similarly less time exploring an object that has remained in place compared to one that has been displaced. RF exposure did not affect the time spent exploring familiar objects that had remained stationary compared to those that had been moved. However, the exposed rats spent less time exploring the ‘old familiar object’ compared to the time spent exploring the ‘recently familiar’ object. The effect was independent of SAR. The authors concluded that the GSM-exposed rats showed an impaired “episodic-like” memory for objects and their order of presentation.

Nordstrom (2009) criticised the interpretation of the study outcome, noting that aged rats of the strain used in this study suffer pronounced retinal atrophy and poor vision. In response however, Nittby et al (2009b) emphasised the importance of touch by the paws, snout and vibrissae in this behaviour.

Genotoxicity

Previously, the IEG has reported that the majority of *in vitro* and *in vivo* studies have not shown genotoxic effects from RF radiation (IEGEMF, 2007). A recent meta-analysis of RF genotoxicity by Vijayalaxmi and Prihoda (2008) supports this view. The authors quantitatively analysed the results from 63 *in vitro*, *in vivo* and human studies published between 1990 and 2005, deriving indices and 95% confidence intervals for various genetic endpoints in relation to frequency, SAR and continuous wave or pulsed RF mostly typical of mobile phone use. They reported that, with few exceptions, the difference between the overall genotoxicity indices for the RF exposed and the sham-exposed and/or control groups was very small; in particular, the mean indices for chromosome aberrations and micronuclei in all groups were within spontaneous levels reported in the historical database.

More recently, Ziemann et al (2009) investigated the incidence of micronuclei in the peripheral blood of mice that had been chronically exposed to GSM-902 or 1747 MHz Digital Cellular System (DCS) radiation for 2 years. Groups of ~100 mice were exposed in a ‘Ferris Wheel’ exposure system for 2 h per day, 5 days per week at whole-body SARs of 0.4, 1.3 and 4.0 W/kg along with concurrent sham-exposed mice, cage controls and a positive control group injected with mitomycin C. In all, approximately 1200 mice were used. There were no significant differences in the frequency of micronuclei between RF exposed, sham-exposed and cage control mice, although there was a significant increase in the positive control group.

Thus, this latest study supports the view that the majority of *in vivo* studies do not show genotoxic effects from RF radiation.

Cancer

Evaluating carcinogenicity in laboratory rodents has remained a cornerstone in identifying agents likely to cause cancer in humans. According to IARC, agents for which there is sufficient evidence of carcinogenicity in experimental animals are considered to pose a probable carcinogenic hazard to humans, unless there is scientific evidence that the agent causes cancer through a species-specific mechanism that does not operate in humans (IARC, 2006). However, despite the similarities in many cancer characteristics between humans and laboratory rodents, interspecies differences need to be taken into account when extrapolating data from rodents to humans.

Classical carcinogenicity bioassays involve exposure of animals over most of their lifetime to the agent being tested. Such studies are potentially capable of revealing whether the tested agent alone could act as a complete carcinogen or serve to increase the incidence of spontaneous tumours. This type of study is, however, not sensitive in detecting weak carcinogenic effects (because of the low number of tumours induced) or co-carcinogenic effects (resulting from their interaction with other carcinogens). To overcome these limitations, experiments have also been conducted combining exposure to RF radiation with exposure to known carcinogens. One such group of studies have examined the effects of RF exposure on 7,12-Dimethylbenze(a)anthracene (DMBA) induced mammary gland tumourigenesis (the DMBA mammary tumour model). Although some indication of enhanced or decreased tumourigenesis have been reported, in general, these findings were not repeated in other experiments by the same group or in studies with similar designs by different groups.

Recently, Hruby et al (2008) treated 100 female Sprague-Dawley rats per group with a single dose of DMBA to induce mammary tumours and then exposed the animals to GSM-900 MHz signals in a study almost identical to an earlier study by Yu et al (2006) (discussed by IEGEMF, 2007). The exposure groups included cage controls, sham-exposed animals and three exposure groups with SARs of 0.44, 1.33 and 4.0 W/kg. The exposed and sham-exposed animals were restrained during exposure. The rats were weighed and palpated weekly for the presence of mammary tumours and were killed at the end of the 6-month exposure period. All mammary glands were examined histologically. In contrast to the earlier study, Hruby et al (2008) found several statistically significant differences between RF field-exposed groups and the sham-exposed group. All RF-exposed groups had, at different times, significantly more palpable mammary gland tissue masses than the sham-exposed group, but there were no differences between the three RF-exposed groups. The incidence of malignant mammary tissue tumours was lowest in the sham-exposed group, and significantly increased in the high exposure group. However, the incidence of benign tumours was significantly lower in the three RF exposed groups than in the sham-exposed group. In addition, the number of animals with benign or malignant tumours was similar in the sham-exposed group and in the three RF-exposed groups. The cage control group had the highest incidence and malignancy of tumours among all groups. Given that the results from DMBA mammary tumour model studies are known to be of somewhat variable consistency, the authors' interpretation was that this was a chance observation. Comparison to the results of the almost identical study of Yu et al (2006) supports this conclusion: both studies reported similar development of mammary tumours in three groups, but lower rate of development

(seen in the appearance of palpable tumours and/or reduced malignancy) in one group. Hruby et al (2008) found the lowest rate of development in the sham-exposed group, while Yu et al (2006) found it in the 0.44 W/kg group. Both studies consistently reported highest incidence of tumours in the cage control group, which is most likely related to the different handling of the cage-control animals in terms of absence of restraint stress, different food intake, etc.

The evidence from this study is interpreted as supporting the view that exposure to RFR characteristic of mobile phone use has no effect on carcinogenesis and that the elevated level of malignant mammary tumours seen in one group was probably a chance observation.

Reproduction and Development

RF effects on development have been reviewed by Juutilainen (2005) who noted that whereas numerous studies have shown that RF fields are teratogenic at exposure levels sufficiently high to cause significant increases in body temperature, there is no consistent evidence of effects following exposure at non-thermal levels.

Dasdag et al (2008) exposed 14 rats and sham-exposed 7 rats to GSM-900 MHz radiation for 2 h per day, 7 days per week for 10 months. The maximum exposure was to the head, and the SAR to the testis was estimated to lie between 0.07 and 0.57 W/kg. A further 10 rats acted as cage-controls. Following treatment, immunohistochemical techniques were used to identify the presence of active caspase-3, a marker for apoptosis, in testicular tissue. The assessment was carried out blind using a semiquantitative scoring procedure. There was no significant effect of prolonged GSM-type RF exposure on levels of apoptosis in the sperm progenitor tissue in the seminiferous tubules of the rat testes compared to levels in sham and cage-control animals.

Sommer et al (2009) investigated the effect of lifetime exposure to UMTS-1966 MHz radiation on reproduction and development over four generations of mice. Thirty groups of ~90 animals (each male caged with two females) were exposed or sham exposed in a set of radial waveguides at power densities of 1.35, 6.8 and 22 W/m² for 24 h per day over their lifetime. The whole-body SAR averaged for each of the three adult animal groups was 0.08, 0.4 and 1.3 W/kg respectively. After mating, one female was killed at 18 days of gestation and scored for corpora lutea, number of foetuses, malformations etc. The first and second litters of each remaining female were assessed for growth and the appearance of developmental markers like eye-opening and righting reflex. Finally, the pups of the second litters (the F1 generation) were weaned, exposed or sham exposed in separate groups of males and females until at an age of 90-110 days when once again each male was placed with two females and exposed or sham exposed. [It should be noted that the averaged whole-body SAR varied depending on the various combinations of pups and/or adults exposed at different stages of the experiment.] This procedure was repeated until shortly before the birth of the F3 generation. The authors found no effect on a number of measures of female reproductive function over the three generations, as assessed from the females sacrificed on day 18, including number of foetuses per litter and number of malformed foetuses per litter. In addition, no effect was seen on the number or weight of the surviving pups, or on the time at which eye opening and the

righting reflex developed. Furthermore, no effect was found over three generations on a number of measures of male reproductive function.

Ogawa et al (2008) examined the effect of exposure to a 1950 MHz W-CDMA RF signal for the International Mobile Telecommunication 2000 (IMT-2000) system on embryo and foetal development in mice. The authors exposed or sham-exposed 60 pregnant mice for 90 min per day from day 7 to day 17 of gestation at average brain SARs of 0.67 or 2 W/kg (whole-body SARs cited as less than 0.4 W/kg); another 20 mice served as cage controls. The mice were sacrificed on gestational day 20 and examined for a number of conventional teratological parameters including the incidence of foetal deaths and visceral and skeletal abnormalities. No statistically significant differences in any parameters either for the health or pregnancy of the dams or for embryo or foetal development. [The analysis of the foetal data was incorrectly based on the number of individual fetuses affected rather than on the number affected per litter which will have underestimated the variance of any parameter, although this is unlikely to have affected an essentially negative outcome.]

These three studies support the view that both acute and chronic multi-generation exposure to RF radiation characteristic of mobile phone use at levels too low to cause significant heating has no effect on reproductive function or development.

Auditory System

Recent animal studies have focussed on possible RF effects on cochlea function per se measuring otoacoustic emission. This is an indicator of the normal mechanical contractility of the outer hair cells of the cochlea and is considered to be a reliable method of assessing cochlea functionality *in vivo*. The outer hair cells, which are notoriously susceptible to various endogenous and exogenous stressors, generate an acoustic signal in response to auditory stimuli (measured for example as the distortion product otoacoustic emission or DPOE), which can be monitored in the external ear canal (auditory meatus).

Following on from earlier work with GSM 900 and 1800 MHz (Galloni et al, 2005a; 2005b), the same group recorded the DPOAE before, during and after the exposure or sham exposure of the right ear of 48 rats to a UTMS-1946 MHz signal at a SAR in the cochlea of 10 W/kg for 2 h per day, 5 days per week for 4 weeks (Galloni et al, 2009). The DPOAE was measured on the Friday before and after exposure and on all Fridays during exposure. Statistical analysis revealed that neither the RF exposure condition nor the interaction between the day of testing and the RF exposure condition was significant. A further 16 animals tested more frequently before, during, and after exposure; again no significant effects were seen. However, effects were seen in a group of positive control animals treated with the ototoxic drug Kanamycin.

The evidence from this study supports earlier observations of a lack of effect of mobile phone type RF exposure on auditory function in rodents.

Endocrine System

Early studies, mostly carried out in the 80s and 90s, have reported that endocrine responses to acute RF exposure are generally consistent with responses to acute non-

specific stressors such as heat (Black and Heynick, 2003); otherwise few effects have been seen.

Lerchl et al (2008) investigated the effect of the prolonged exposure to TETRA (383 MHz) or GSM (900 and 1800 MHz) RFR on melatonin levels in Djungarian hamsters. The authors exposed or sham exposed a total of 240 hamsters either to 383 MHz, 900 MHz, or 1800 MHz RFR for 24 h per day for 60 days at a whole-body average SAR of 80 mW/kg (ICNIRP's 1998 limit on whole-body SAR for members of the public). No effects were found on circulating or pineal melatonin levels following chronic exposure to TETRA or GSM radiation.

Immune System

Heat-related effects on components of the immune system and their function have also been described in early studies of the effects of RF exposure (Black & Heynick, 2003). However, a series of Russian and Ukrainian papers, published in the 70s and 80s, reported that prolonged exposure to RF radiation at relatively low power densities could adversely affect the rat immune system (see Poullietier de Gannes, 2009b). In particular, it was reported that 30-day whole body exposure to 2375 MHz CW at 5 W/m² evoked a pronounced autoimmune response compared to sham-exposed animals and that brain extract from exposed rats would affect the developmental outcome when injected into non-exposed female rats on day 10 of pregnancy. Such findings formed part of the basis of RF guidelines in the former USSR.

Recently, Veyret, Lagroye and colleagues (Poullietier de Gannes et al, 2009b) have attempted to confirm these findings using modern dosimetric and biological methods. In particular, the authors measured levels of a number (16) of circulating antibodies for antigens marking a wide range of potential tissue changes, including those resulting from autoimmune responses and others indicating neurodegenerative changes, in rats (16 per group) exposed for 7 h per day, 5 days per week, for a total of 30 days, to 2450 MHz CW at 5 W/m² (a whole body SAR of 0.16 W/kg). The rats were killed 7 or 14 days after exposure; all the rat sera were coded so that the results could be scored blind. In addition, coded sera from exposed and sham-exposed rats were injected into two groups each of 20 rats on day 10 of pregnancy; the foetuses were examined on day 18 of gestation for developmental outcome using standard teratological methods. No effects were seen on any of these endpoints, suggesting the absence of any autoimmune responses or degenerative effects.

Conclusions on animal studies

A number of studies focussed on effects on brain structure and function. Several studies reported an increase in gene expression and other biochemical changes in brain tissue but the evidence was rather weak; in two studies, the positive results might be attributable to heating. A number of studies by Salford and colleagues reported an increased permeability of the blood-brain barrier and an increase in neuronal damage following low level exposure to GSM mobile phone radiation. However, these results have not been confirmed by studies from three other laboratories. In terms of behavioural function, a study reported that rats chronically exposed to GSM-type mobile phone radiation showed an impaired episodic-like memory for familiar objects. In view of an earlier study

reporting an absence of such effects except following thermal exposures, some attempt at confirmation is necessary.

Otherwise, no effects have been seen in a study of genotoxicity in chronically exposed mice. An elevated level of malignant mammary tumours seen in a study of the effects of GSM RF radiation on the incidence of chemically induced mammary tumours in rats was probably a chance observation; this tumour model is known to be variable and the results were not supported by those of another, almost identical study. A number of recent studies have reported a lack of effect of mobile phone type RF radiation on reproductive function or development. No effects of 900 or 1800 MHz GSM RF have been reported on cochlea function or on melatonin circulation. Finally, Veyret and colleagues at Bordeaux University have been unable to confirm Russian and Ukrainian reports of impaired immune function following prolonged low level exposure to 2450 MHz radiation.

Overall, it can be concluded that recent animal studies have not identified any clear effects on a variety of different biological endpoints following exposure to RF radiation typical of mobile phone use, generally at levels too low to induce significant heating. These results are consistent with previous conclusions of the IEG. However, further important studies are in progress. These include a large National Toxicology Program study of the effects of sub-chronic and chronic exposure to 900 MHz and 1900 MHz CMDA or GSM RF radiation on spontaneous tumours in rats and mice, due to be completed in 2014 (<http://ntp.niehs.nih.gov>; Sept 2009). In addition, several studies are in progress at the PIOM laboratory at Bordeaux investigating whether exposure to RF fields related to wireless communication such as Wi-Fi has the potential to adversely affect the immune functions of immature mice and central nervous system histopathology and reproductive function in immature rats (www.cost281.org/download.php?fid=1068).

Human laboratory studies

Experiments using volunteers exposed to RF are restricted for ethical reasons to the investigation of transient physiological phenomena which, in the controlled conditions of a laboratory, are at relatively low exposure levels. It is possible, however, that effects judged to be harmless when experienced transiently in the laboratory, may have adverse health consequences if experienced for long periods in an occupational or public context. The advantage of such experiments is that they indicate the likely response of other people exposed under similar conditions, but the disadvantages include the often short duration of investigation and the small number of subjects usually examined. To some extent, shortcomings such as heterogeneity in the study population can be addressed through experimental design, in this example by using a crossover experimental design (see below), or retesting of participants to account for possible differences in response. However, due to practical considerations, subjects have tended to be relatively homogeneous and are therefore unlikely to reflect the range of variability encountered within a population. Nevertheless, within this limited context, volunteer studies can give valuable insight into the physiological effects of exposure in normal, healthy people.

Important factors in the experimental design of many recent studies include the use of double-blind procedures and crossover and counter-balanced protocols. Double-blind procedures apply when both the experimenters and subjects are unaware of the exposure status of the subjects, and so are less likely to be influenced by any expectation of a

particular outcome; single-blind procedures, often used in early studies, are where only the subject is unaware of their exposure status. A crossover design is where subjects are both exposed and sham exposed in different parts of the experiment, so that they act as their own controls (also known as a within-subjects or repeated measures design). This procedure minimises the effects of intrinsic differences between subject groups, such as might occur between a sham group and an exposed group, which could affect the experimental outcome. A counter-balanced protocol is where all possible orders of exposures are used, with equal numbers of subjects experiencing each order. This counteracts any effect of time-dependency on the subjects' responses, resulting for example from improving in task performance or from loss of attention during the course of a study.

The previous report from the IEG (IEGEMF 2007) summarizes the findings on neurocognitive functions and subjective symptoms as follows: "In general, the recent, methodologically rigorous studies do not replicate the positive findings from smaller, less rigorous studies published a few years ago, but a few positive effects are reported". The present report continues the same line with only a few exceptions.

Brain electrical activity

EEG

Some recent studies have targeted the EEG (electroencephalography), reflecting the continuous electrical mass-activity of the neural tissue, in waking subjects while performing a cognitive task, or just in resting state. The results are rather uniform.

Hinrikus et al. (2008 a, b) evaluated the effect of microwave EMF (450 MHz, SAR1 g = 0.303 W/kg) modulated at different frequencies (7-21 Hz; 2008b), (7-1000 Hz; 2008a) on human EEG rhythms in 13 (2008b) and 66 (2008a) subjects. The design was both within (2008b) and between subjects (2008a). Both studies showed that the effect of microwave EMF on EEG is seen in alpha and beta bands, the effect depends on modulation frequency, and that there are considerable interindividual differences in effects of EMF on EEG. The major finding in the first report (Hinrikus et al., 2008b) was an increase in the average EEG alpha (17%) and beta (7%) power, while theta rhythm remained unaffected. The enhancement was dependent on the modulation frequency, 14 and 21 Hz being most effective, in contrast to the lower 7 Hz. The second study (Hinrikus et al., 2008a) with a larger array of modulation frequencies (7-1000 Hz) showed increased EEG energy (beta power analyzed) by microwave exposure in 7 out of 19 subjects at 7 Hz modulation frequency, 4/13 subjects at 14 Hz modulation frequency, 3/19 at 21 Hz modulation frequency, 3/15 subjects at 40 Hz modulation frequency, 2/15 subjects at 217 Hz modulation frequency, and 0/19 subjects at 1000 Hz modulation frequency. These results thus demonstrate the EEG power/energy increment being dependent on the modulation frequency of the microwave radiation, but also varying considerably between individuals, and being evident only in a minority of the participants in the study. The importance of this study lies in the analysis of individual subjects' EEG-responses instead of just reporting the average changes. The behavioural counterpart of these EEG frequency modulations is completely unknown, if non-existent.

Croft et al. (2008) exposed 120 adult subjects in a double-blind counterbalanced crossover design to an 875 MHz GSM phone (0.25 W mean) modulated by 217 Hz (spectrum analysis of phone emissions revealed also 16 Hz frequency possibly due to the battery operation), and assessed the EEG in the first and last 10 min of a 30-min exposure. The phones were positioned on either the left or the right side of the head. An increased power in the alpha band was found, which was larger on the ipsilateral compared to the contralateral side in posterior regions. Thus, we can see the similar type of effect of modulated GSM EMF as Hinrikus' group demonstrated for modulated microwave EMF.

Interestingly, Cook et al. (2009) applied pulsed ELF (Extremely Low Frequency) EMF and further measured resting EEG from 32 participants in a crossover study. They found increased alpha activity after approximately 5 min of exposure, which is also consistent with their previous results.

Kleinlogel et al (2008a) evaluated the effects of both 900 MHz GSM (pulse-modulated at 2-1736 Hz; 1 W/kg) and 1950 MHz UMTS (SAR 0.1 and 1 W/kg) signals on vigilance controlled resting EEG in 15 subjects in a double-blind, randomized, crossover test procedure. In contrast to the aforementioned studies, no effects were found on any of EEG frequency bands (also the well-being of the subjects was measured, and was not found to be affected).

Finally, a methodological study (Hountala et al., 2008), aimed at developing new approaches to analyzing EEG, but also applying EMF exposure as a test whether the analyses are powerful enough to reveal very small effects. They addressed the spectral power coherence of the EEG with a new methodological analysis, and used 900 (N=19) and 1800 (N=20) MHz EMF (non-modulated) exposure on and off sessions as test template while the participants were performing an auditory memory task. The design was single blind, crossover, and counterbalanced. They found delta coherence to be affected by the EMF, and also a curious gender effect: in the absence of radiation, males exhibited higher overall spectral power coherence than females, whereas these differences disappeared in the presence of 900 MHz and were reversed in the presence of 1800 MHz. Statistical analyses seem to be adequate, but still this rather peculiar finding on gender differences definitively calls for replication.

To summarize, pulse-modulation at lower frequencies seems to increase the power/energy of alpha and beta frequency bands of the human EEG in most of the studies quoted here (see also the Sleep section). This is a phenomenon that so far does not have any behavioural counterpart; there is a growing scientific evidence against EMF effects on human cognitive functions (pulse-modulated GSM signals; also a comparison of pulsed and non-pulsed GSM EMF- induced effects by Haarala et al., 2007). The measured effects may be an epiphenomenon due to the interaction between EEG recording and pulse-modulation, and this could be well studied in animal models or *in vitro* nerve cell cultures.

Auditory Brain stem Responses (ABRs) and Event-Related Potentials (ERP)

The ABRs are very short-latency event-related evoked responses, averaged from the EEG, which reflect the activations of the nuclei along the auditory pathways. Stefanics et

al. (2007) exposed their subjects (N=26-30, final number unclear) with 900 MHz (SAR 0.41 W/kg at 3 cm depth) in a double-blind, between subjects study. They determined the effects of exposure on waves I, III, and IV of auditory brain stem responses (ABRs), not simultaneously but after the exposure. No effects were found.

Kwon et al. (2009a) exposed 17 subjects to GSM mobile phone EMF (902.4 MHz pulsed at 217 Hz, (SAR 1.20 W/kg) simultaneously with ABR measurements in a single-blind study. No effects were found.

The ERPs are longer-latency event-related evoked responses, averaged from the EEG, that reflect processing of the sensory, e.g. auditory, stimuli, and various cognitive processes (perception, recognition, attention, various memory processes) involved in the process. Kwon et al. (2009b) measured a specific component of the auditory ERP, mismatch negativity (MMN), which is possibly the most sensitive cortical measure of automatic auditory change discrimination. The MMN was measured in 17 healthy volunteers during actual or sham exposure (double-blind) from a 902 MHz GSM mobile phone, inducing a SAR of 1.21 W/kg (2x6 min/each side). No effect of exposure on MMN was observed.

Exactly the same MMN paradigm and similar exposure was then applied to 17 children of 11-12 years of age (Kwon et al., 2009c). No effects of the exposure were found, but the authors state that the study only had statistical power for detecting only large effect sizes.

Kleinlogel et al. (2008b) reported no effects of both GSM and UMTS signals (see above) on the auditory ERP cognitive components N100 and P300 (N=15) elicited in an oddball paradigm in a crossover, double-blind study. Related behavioural measures also did not show any effect of the exposure.

Stefanics et al. (2008) also exposed 29 healthy volunteers for 20 min to the signal from a UMTS mobile phone and investigated the cognitive components of the auditory ERPs while subjects were performing an oddball task. The design was double-blind and counterbalanced, and valid statistical tests were applied with corrections for multiple comparisons. No effects of exposure were observed.

In sum, the EEG/ERP studies reviewed indicate that there is some evidence for effects of exposure to a GSM- or microwave-type signal on the spontaneous EEG. The large study by Croft et al. (2008) has confirmed previous findings of increased power in the alpha band (8–12 Hz) of brain activity. The studies by Hinrikus et al. (2008a, b) on 450 MHz microwave radiation have given more evidence of the effect of pulse modulation and its frequency, also reported in other studies, on alpha and beta bands. The behavioural counterpart of these phenomena is unknown. In contrast, several methodologically rigorous studies now demonstrate that mobile phone EMFs are non-detectable by short-latency (ABR) or longer-latency cognitive ERPs.

Cognition

The previous report from the IEG (IEGEMF 2007) concluded that all cognitive studies reviewed had negative results, i.e., no effects on cognitive functions were observed. "The recently published cognitive studies are mostly negative: several report a lack of effects from both pulsed and CW RF radiation". The previous report also recommended double-

blind, crossover (within subjects or repeated measures), and counterbalanced designs. Since the previous report some further studies on GSM and UMTS RF and cognitive functions have been published.

Curcio et al. (2008) failed to replicate with 24 subjects their previous findings on reduced simple RTs. Also an additional motor (sequential finger tapping) task failed to show any effects of the 902.4 MHz field modulated at 217 Hz with average power of 0.25 W, SAR=0.5 W/kg, cumulative effect of 3x15 min exposures in a double-blind, counterbalanced setup.

Regel et al. (2007a, 2007b) found no effects of GSM 900 MHz (SAR 10g=1 W/kg; 2-1736 Hz modulation) in simple and choice RT tasks. They also reported inconsistent results in n-back memory tasks: first improved performance (reduced RT, enhanced accuracy) in Regel et al. (2007a; N=24), but then the opposite result (increased RT with increasing SAR levels) in Regel et al. (2007b; N=15). Corrected p-values were applied.

Fritzer et al. (2007) examined long-term cumulative effects by exposure with a 900 MHz GSM (modulation frequencies 2, 8, 217, and 1733 Hz; 28.5 W peak, SAR1g=0.875 W/kg head, 0.024 W/kg whole body) of 2 h daily exposure for four weeks (between subjects, N=10+10) and exposure during 8 h night sleep for six nights (within subjects). No significant effects were found on attention, memory, or executive functions in this single-blind study.

Irlenbusch et al. (2007) found no effects in the visual discrimination threshold in their single-blind crossover study on 33 subjects with GSM 902.4 MHz (modulation 217 Hz) exposure (1 W/m²; SAR1g=0.007 W/kg, SAR 10g=0.003 W/kg, both at retina).

Luria et al. (2009) studied GSM (915 MHz, modulation 217 Hz, 0.25 W mean) effects in crossover, single blinded design on 48 subjects performing spatial working memory task, but found no effects after (Bonferroni) correction for multiple comparisons.

Cinel et al. (2008a) studied in a large sample (N=160 and 168, in two studies) effects of GSM EMF (888 MHz, unmodulated, SAR=1.4 W/kg ±30%) on short-term memory and vigilance and then short-term memory and attention with both between and within subject, double blind, counterbalanced design. Even though corrections for multiple comparisons were not applied, results did not reach statistical significance.

Wiholm et al. (2009) studied spatial behaviour and learning (a virtual Morris water-maze) in subjects with (N=23) and without (N=19) symptoms related to mobile phone use. The design was both double-blind and crossover, and the exposure (884 MHz, varying discontinuous and non-discontinuous transmission modes, SAR10g=1.4 W/kg) lasted for 2.5 hours. Spatial performance was measured before and after the exposure and the order of sessions was counterbalanced. The authors claim that the symptomatic group improved their performance during RF exposure (slightly deviating performance of the symptomatic group on one trial out of seven). The authors themselves state that there is a need for replication.

3G UMTS signals (1.97 GHz, varying exposure level) were not found to affect reactions or attention in a double blind, pseudorandomized crossover study with 40 subjects by Unterlechner et al. (2008).

In a study by Riddervold et al. (2008) two groups of healthy subjects aged 15-16 years (N=40) and 25-40 years (N=40) were exposed to a UMTS base-station-like signal (2140 MHz, exposure level 1 V/m) and sham exposure, each lasting for 45 min. Cognitive performance (simple and complex RT, Rapid Visual Information Processing, and Paired Associated Learning from CANTAB -test battery) was determined during each 45-min exposure/sham, but no effect was observed in either age group.

Furubayashi et al. (2009) exposed female subjects with mobile phone related symptoms and controls to a UMTS-like (WCDMA 2140 MHz base station) signal. The 30-min exposures did not induce any effects on the cognitive performance (pre-cued choice reaction time) and autonomic functions measured.

To summarize, various aspects of perception, attention, memory and executive functions have been covered in the cognitive studies so far. The issue of multiple comparisons was not taken into account in the earlier behavioural studies, which resulted in reporting some significant results that possibly were due to statistical noise. Indeed, later more elaborated studies could not replicate these results. Therefore, regarding human cognitive functions and the (limits of the) different measures for them, mobile phone or base station radiation does not seem to have effects (regardless of pulse-modulation, cf. EEG) on cognitive functions assessed with the measures for them. The effects, if any, are simply not large enough to be measurable with the existing tools of cognitive psychology.

Sleep

In a total of ten previous studies the effects of RF exposure on sleep parameters and sleep EEG has been targeted. The results have been rather inconsistent due to small samples and other methodological difficulties, and no replications of the previous studies or new studies targeting the sleep parameters and sleep EEG have emerged so far.

Regel et al. (2007b) reported a dose-dependent relation between the strength of the EMF (GSM handset-like signal, 900 MHz with modulation at 2-1736 Hz; 0.2 and 5 W/kg) and increase of the power in the slow (10.75-11.25 Hz) and fast spindle frequency range (13.5-13.75 Hz) of the non-REM sleep EEG in 15 healthy male subjects after 30 min exposure before sleeping (but filled with cognitive tests; for results see Cognition). The finding on the dose-dependency of the EMF effect could be rather strong evidence for an RF effect on electrical activity of the brain, but the frequency bandwidths with significant effect reported are very narrow (0.5 and 0.25 Hz). This strongly refers to the possibility of the result being just a random difference in EEG during different conditions, and the measurements should be replicated. Interestingly, here again the pulse modulated RF EMF seems to affect (if the effect is real) EEG in the alpha and low beta range (cf. EEG).

Subjective symptoms

The previous report from the IEG (IEGEMF 2007) concluded: "With regard to hypersensitivity, the recent studies examining the effects of GSM and UMTS RF radiation support the observation made previously (IEGEMF 2006) that RF-sensitive individuals report symptoms of greater severity than non-sensitive individuals, but these are not correlated with exposure and may reflect the conscious expectation of such effects". This effect is generally called *nocebo*.

The most effective means, although sometimes ecologically not so valid, for targeting the subjective symptoms, or ability to detect the presence of EMF, are provocation studies in a laboratory environment with accurate exposures, accurately measured SAR, and controlled designs. With this approach both healthy volunteers from the general population and subjects with EMF-related hypersensitivity have been studied.

Kwon et al. (2008) recruited 84 volunteers to participate in a study where a 50 € award could be earned by those who could tell with at least 0.75 probability whether the GSM EMF (902 MHz pulsed at 215 Hz; SAR_{1g}=1.28 W/kg, SAR_{10g}=0.82 W/kg) was on or off, or whether it changed (on-off, off-on). The design was crossover and double-blind with counterbalanced order of session. Nobody, including six subjects with self-reported EMF sensitivity, won the prize. Instead, the study revealed that a very high rate of correct responding can be achieved by chance (by two subjects both in one session out of six), but the result could not be replicated. Another important finding was that the result obtained can be shaped to a considerable degree by varying the setup and the subjects' task, which both affected the subjects' strategy in the specific task.

Augner et al. (2009) studied the short-term effect of mimicked GSM base station in a field laboratory on subjective well-being (good mood, alertness, calmness). The design was between subjects (57) and double-blind, and the conclusion was rather opposite to all other studies: "Short term exposure to GSM base station signals may have an impact on well-being by reducing psychological arousal".

Cinel et al. (2008b) did a double-blind, between subjects, counterbalanced study with a large number of subjects (N = 496) with GSM exposure (modulated and non-modulated; the average SAR for both modes = 1.4 W/kg \pm 30%). Participants evaluated different subjective symptoms and their location in the face and head area on a 5-point Likert scale. For only one group of participants (N=160) dizziness was found to be affected by GSM exposure. The authors conclude that no consistent evidence was found for the exposure to mobile phone RFR to induce subjective symptoms.

Riddervold et al. 2008 used a randomized, double-blinded cross-over design to expose healthy subjects to a UMTS base-station-like signal (2140 MHz signal modulated as UMTS, exposure level 1 V/m) and sham exposure. 40 adolescents of 15-16 years of age and 40 adults of 25-40 years of age participated in the study. At the beginning and the end of each 45-min exposure/sham session a questionnaire on self-reported symptoms and perceptions of air quality was completed. No effect on symptoms and perceptions was observed for either age group separately. An increase in headache was found after UMTS exposure compared to sham when both age groups were combined, but the baseline levels for the groups differed.

The topic of hypersensitivity in the context of provocation studies has been recently reviewed by Rössli (2008), who covered 30 reports from 2001-2008 in his review. His conclusions can be quoted as follows "Some of the trials provided evidence for the occurrence of placebo effects [...]. This review showed that the large majority of individuals who claims to be able to detect low level RF EMF are not able to do so under double-blind conditions. If such individuals exist, they represent a small minority and have not been identified yet. The available observational studies do not allow differentiating between biophysical from EMF and placebo effects".

Rubin et al. (2009) also reviewed recently results from 46 provocation studies (including 1175 EHS participants) on what they call "Idiopathic Environmental Intolerance" (IEI) attributed to electromagnetic fields, formerly "Electromagnetic Hypersensitivity". Their conclusion is the same as by Rösli (2008), "[...] the studies included in the review did support the role of the placebo effect in triggering acute symptoms in IEI-EMF sufferers [...] repeated experiments have been unable to replicate this phenomenon (symptoms being triggered by electromagnetic fields) under controlled conditions". The provocation studies published after the previous report by the IEG (IEGEMF 2007) reviewed here do not bring anything new to this conclusion.

Hillert et al. (2008) exposed 38 participants with self-reported mobile phone related symptoms (headache or vertigo), and 33 non-symptom participants with 884 MHz GSM handset (exposure signals simulating conversation) versus sham for three hours. The design was a double-blind, crossover study. Symptoms were scored on a 7-point Likert scale before, in the middle and just prior to the end of the exposure. Subjects also reported their belief of actual exposure status. According to the authors, "the results showed that headache was more commonly reported after RF exposure than sham, mainly due to an increase in the non-symptom group. A belief that the RF exposure had been active was associated with skin symptoms."

Furubayashi et al. (2009) replicated the study by Riddervold et al. (2008) but with EHS participants. They exposed 11 female subjects with mobile phone related symptoms and 43 controls to a UMTS-like signal (2.14 GHz at 10 V/m). Double-blind crossover design was applied and the exposure lasted 30 min being either continuous, intermittent or sham. Several psychological (personality traits) and cognitive (pre-cued RTs) parameters were measured before and after exposure, autonomic functions were monitored, and perception of EMF and level of discomfort were determined. No effects of exposure were observed on any of the investigated parameters. The subjects with mobile phone related symptoms did experience a higher level of discomfort than the controls, but this was independent of the type of exposure.

Rubin et al. (2008) investigated the occurrence of symptoms using a questionnaire in three groups: 52 subjects who reported sensitivity to mobile phones, 19 subjects who reported sensitivity to mobile phones as well as to other electrical devices (self-proclaimed electrosensitives), and 60 subjects as control group without such attributions. Well-being in those who proclaimed being electrosensitive was lower than in the subjects who reported being sensitive to mobile phones but did not claim to be electrosensitive, or in controls without symptoms.

Nieto-Hernandez et al. (2008) studied the possible impact of feedback of the ability to discriminate an active mobile phone signal from a sham signal on the perceived sensitivity reported by participants who described being sensitive to mobile phone signals 6 months after the initial sessions with the feedback. Fifty-eight participants (69 originally) participated in the follow-up, and no difference in sensitivity scores or symptom severity scores were found among the individuals who were told that they were correct (N=31) or incorrect (N=27) in their perceptions.

Finally, there are two studies with applications of recent strong tools from cognitive neuroscience, i.e., functional brain imaging (Landgrebe et al., 2008a), and artificial neural

network stimulation (Landgrebe et al., 2008b). Landgrebe (2008a) applied functional MRI (fMRI) to study brain activity during sham exposure (no EMF on) to a mobile telephone in a group of 15 EHS and 15 control subjects. In the EHS subjects, the areas of the brain that are activated during sham exposure or when anticipating the exposure were the same as those activated in both EHS and non-EHS subjects when they are exposed to heat, used as control stimulation. These activations possibly are related to mechanisms of placebo and nocebo effects, both related to subjective well-being. Landgrebe et al. (2008b) applied a very interesting methodological approach to EHS, namely sensitivity to TMS pulses applied to dorsolateral prefrontal cortex vs. sham stimulation of 87 EHS and 107 age- and gender-matched controls. The design was double-blind. Health status and EMF-related cognitions were evaluated using standard questionnaires, and the evaluations specifically differentiated EHS from their controls. The objective TMS sessions revealed that in sham stimulations 60% of the EHS but also 40% of the controls reported sensations, whereas the perception thresholds for real magnetic pulses were comparable in both groups (median 21% versus 24% of maximum pulse intensity). Intra-cortical facilitation was decreased in younger and increased in older EHS. The authors conclude that the results demonstrate significant cognitive and neurobiological alterations pointing to a higher genuine individual vulnerability in electromagnetic hypersensitive patients. The results from TMS versus sham conditions, the similarity of TMS thresholds in EHS and controls, and the odd variation in intra-cortical facilitation in EHS as a function of age, may render the conclusions somewhat exaggerating.

To summarize, provocation studies of subjects both with and without subjective symptoms and EHS/IEI come to the same negative conclusions, and continuing this approach probably does not lead to any new findings. Instead, the importance of the nocebo-effect has been emphasized in several recent studies and reviews. Also the application of the new neuroscience research tools, functional brain imaging and TMS, are very promising for targeting the placebo- and nocebo-mechanisms in the human brain.

Some general methodological issues and final conclusions on human laboratory studies

The previous report from the IEG (IEGEMF 2007) recommends double-blind, crossover (within subjects or repeated measures), and counterbalanced design. Three other issues should be included. First of all some earlier studies reported false positive results due to lack of corrections for multiple comparisons in statistics. Replication of the studies has commonly not yielded positive results, and therefore all studies with small sample size and vague statistics, and chance-like results should be replicated. Finally, the results should include, in addition to p-values, also effect sizes. This is crucial information for evaluation of the credibility of the results, and the golden standard in publications in cognitive psychology and cognitive neuroscience today.

Almost all experimental studies reviewed here are provocation studies with rather short exposures. Based on the results it can be concluded that cognitive and ERP/ABR studies with short-term exposures do not bring anything new to our knowledge. These methods simply are too crude or the phenomena studied too small or non-existent to be revealed.

Therefore research should target long-term exposures and different user groups with different amounts of getting exposed to the EMF.

Surprisingly few studies are available on children. Since the previous report from the IEG (IEGEMF 2007) only one ERP study on children has been published (Kwon et al. 2009c). In the light of all official recommendations in different countries with special emphasis on children's use of mobile phones, this is rather peculiar. We need more scientific data on longer-term exposure effects on children. Gender does not seem to play any role in EMF effects, but no thorough review on this topic is available.

Finally, EEG alpha- and beta-frequencies seem to be sensitive to modulation by some pulse-modulation frequencies of the RF signals. This curious effect does not have any behavioural counterpart, since similar types of EMF has been applied in various behavioural studies with negative results. The effect on EEG power/energy within these EEG frequencies can be an epiphenomenon due to interactions between exposure system and EEG- measurements, and it could be studied directly in biophysics laboratories.

Epidemiological studies

Mobile phone studies

Interphone

This report covers studies published since our previous report as well as those not detailed previously and includes an analysis based on the French, Japanese, Israeli, UK, and Finnish Interphone results, as well as two pooling efforts based on a combined Nordic and UK parts of Interphone.

The French INTERPHONE Study of mobile phone use and risk of glioma, meningioma and neuroma has been published in French, with an extensive English-language abstract (Hours et al, 2007). For the French study, subjects had to be residents of Paris or Lyon. Subjects with different tumour types were recruited at different times during the study period for the French study. Controls were randomly selected from voting lists and matched to cases on gender, age (5 yr) and residence. Four hundred fifty-five controls and 350 cases, including 96 gliomas (96 controls), 145 meningiomas (145 controls) and 109 neuromas (214 controls) participated. Exposure information was obtained by personal interviews, with participation of 78% for glioma cases, 60% for meningioma, 81% for acoustic neuroma, and 75% among controls. Of the controls, 56% had used a mobile phone regularly. Regular cell phone use was not associated with an increased risk of glioma, OR=1.2 (0.7-2.1), meningioma, OR=0.7 (0.4-1.3) or acoustic neuroma OR=0.9 (0.5-1.6). Among 21 glioma cases with use of longer than 3.8 years an OR of 2.0 (0.7-5.2) was reported. Similar increase was seen in the highest categories of cumulative talk time and cumulative number of calls. However, these results are limited by small numbers and comparatively short history of mobile phone use.

The Japanese Interphone study has reported the results on brain tumours (Takebayashi, et al. 2008). The cases were 83 incident glioma cases, 128 meningioma cases, and 101 cases of pituitary adenomas aged 30-69 years and diagnosed in 2000-2004. The authors recruited up to 4 controls per case using random digit dialling, and matching within 5 year on age, sex and residence. Exposure information was obtained by personal

interviews, with participation of 59% for glioma cases, 78% for meningioma, 76% for pituitary adenomas, and 51% among controls. Of the cases, 52% - 65% had used mobile phones regularly, and the corresponding figure was 53% for controls. In addition to the standard Interphone protocol to assess mobile phone use, this study attempted to estimate the maximum SAR value inside the tumour. Regular mobile phone use was not associated with increased risk: glioma=1.2 (0.6-2.4), based on 56 cases; meningioma=0.7 (0.4-1.2), based on 55 cases; pituitary adenoma=0.9 (0.5-1.6), based on 62 cases. The OR for cumulative use 10 years or longer was 0.6 for glioma based on 2 cases, 1.4 for meningioma based on 4 cases, and 1.2 for pituitary adenoma based on 4 cases. No increased risk was observed for the ipsilateral use. For the SAR-based analysis, they observed an OR of 5.8 (0.96-35.6) based on 7 glioma cases and 4 controls) with cumulative max SAR-hour greater than 10 W/kg-hour. The study was relatively small and participation among controls rather low. The number of long-term users was also relatively small.

The Israeli Interphone study has reported results on benign and malignant parotid gland tumour risk (Sadetzki, et al. 2008). Extending the age range from 30 to 59 years, in all, 460 subjects with confirmed tumours (58 malignant, 264 pleomorphic adenoma, 117 Warthin's tumour, 21 others) diagnosed in 2001-2003 were included. All of the participating 1266 controls (of up to 7 controls per case) using a post hoc matching were included. Eighty four (malignant) to 87% (benign) of cases participated, while the participation rate among controls was somewhat lower (66%). Of the controls, 55% had used mobile phones regularly. Adjustments were made for the reported use of hands-free kits. Overall, no increased risk of parotid gland tumour for any of the exposure measures, including regular use, time since start of use, duration of use, cumulative number of calls, and cumulative call time was observed. For example, OR=1.1 (0.5-2.1) for malignant tumours and 0.9 (0.6-1.1) for benign based on ever/never use comparison. However, based on subgroup analyses (regular use, rural areas, and particularly ipsilateral use) the group concluded that their results suggest an association between mobile phone use and parotid gland tumours. For example, the odds ratios for above-median ipsilateral use were: 1.6 (1.1-2.2) for cumulative number of calls and 1.5 (1.1-2.1) for cumulative call time. The corresponding results for contralateral use was 0.8 (0.5-1.2) and 0.8 (0.6-1.3), respectively.

Part of the UK INTERPHONE study on pituitary tumours diagnosed between 2000 and 2005 has been published (Schoemaker et al, 2009). Two hundred and ninety one cases were 18-59 years of age and 630 controls were selected from general practitioner lists. The participation rates were 63% for cases and 43% for controls. Sixty percent of cases and 61% of controls were classified as regular phone users in the period at least 1 year prior to the reference date. The OR for regular use was 0.9 (0.7-1.3). Odds ratios were around unity for nearly all indices of phone use, including duration of use, time since first use, or cumulative number of calls or hours of use. Subjects who had more than the median hours of use (51 hours) 10 or more years prior to diagnosis had an odds ratio of 1.6 (0.8-3.6). Authors note that recall bias and selection bias may be present, because pituitary tumours are usually benign and frequently undiagnosed and may have been present a long time before diagnosis.

Hartikka and colleagues (2009) analyzed a subset of the Finnish Interphone study (slightly more than half of the study sample) with a focus on the part of the brain most heavily exposed to radiofrequency electromagnetic fields from mobile phone use. In a case–case analysis of glioma the distance between the tumour and the presumed location of the mobile phone was examined. Ninety-nine glioma cases were identified from the neurosurgery clinics of Helsinki and Tampere university hospitals in Finland during the period 2000 to 2002. The exposed cases were those with the tumour mid-point (defined from radiological imaging) within 4.6 cm from the line between the mouth and the external meatus of the ear, representing the most likely location of the mobile phone. A slightly higher proportion of gliomas among mobile phone users than non-users occurred within 4.6 cm from the presumed location of the mobile phone (28% vs. 14%). Modestly elevated odds ratios were observed for several indicators of mobile phone use, but the highest odds ratios were found for contralateral and short-term use. This approach minimizes both recall and selection biases likely present in all Interphone studies. However, these results are limited by the small sample size and inability to account for substantial variability in the field strength depending on the characteristics of the phone, network and environment.

Lahkola et al (2007) performed a pooled analysis of glioma based on Interphone data from Denmark, Finland, Norway, Sweden, and Southeast England. Included were 2530 glioma cases diagnosed during the period 2000 to 2004, as well as 6581 controls matched for age, sex, and region of residence. The participation rates for cases and controls were 60% (with a range for individual studies of 37-81%) and 50% (with a range for individual studies of 42-69%) respectively, leaving 1521 cases and 3301 controls in the final analysis. The vast majority of controls (92%) used mobile phones and 59% of controls were regular users. Most estimates of risk were at or below unity; for ever use of a mobile phone the OR was 0.6 (95% CI 0.5-0.8); for regular phone use 0.8 (95% CI 0.7-0.9); for lifetime years of use 1.0 (95% CI 0.97-1.0) per year, and for various measures of cumulative use. For ipsilateral use for 10 or more years since first use the OR was 1.4 (95% CI 1.0-1.9); the corresponding result for contralateral use was 1.0 (95% CI 0.7-1.4). While based on a large number of cases, the study was limited by the low participation of controls which could result in selection bias, and recall bias (for example seen in reduced risk for contralateral use for shorter durations of use where no association would be expected). Of course questionnaire-based estimation of exposure is subject to large misclassification and likely differential recall by cases and controls.

Similar to the glioma results presented above, Lahkola et al (2009) performed analyses of pooled data from Nordic and UK Interphone studies for meningioma. The participation rates for cases were 74% (ranging from 55 to 90% in individual studies) and, as indicated before, 50% for controls, resulting in 1204 cases and 2945 controls included in the analysis. Again many of the estimates of risk were below unity, e.g. for regular phone use the OR was 0.8 (95% CI 0.7-0.9). There were no indications of risk even among subsets of ipsilateral and contralateral use among long term users.

Other mobile phone studies

In a case-control study (Stang et al. 2009), earlier results suggesting an association between mobile phone use and uveal melanoma could not be confirmed. The new study

evaluated exposure more extensively, the earlier focusing only on mobile phone use at work. Also, the sample size was substantially larger with 455 cases and 827 population controls in the current analysis. Three groups of controls were used: population-based, clinic-based and siblings. Participation was >90% for cases and >50% for all sets of controls. Exposure assessment was based on the Interphone questionnaire. Odds ratios related to regular mobile phone use ranged from 0.7 (95% CI 0.5-1.0) with population controls to 1.2 (95% CI 0.5-2.6) with sibling controls. No exposure-effect relation was seen in analyses by duration of use or cumulative call-time. The odds ratios tended to be higher in comparisons with clinic controls than population controls. Limitations include small numbers of long-term users (3% of cases and 2% of population controls) and possible selection bias due to more common mobile phone use among participating than refusing controls. Based on probabilistic bias analysis, the authors concluded, however, that this would not account for the lack of association.

Incidence of neurological disease has been analyzed in the Danish cohort study of mobile phone use (Schuz et al. 2009). The cohort consisted of 420,000 persons (85% men) with subscription to a mobile phone provider that started before 1995 (mainly early 1990s). Follow-up extended through 2003, but median length of follow-up was not reported. Disease incidence was assessed based on the nationwide hospital discharge database. Indirect standardization was used with results reported as standardized hospitalization rates (SHR, observed/expected rates). A slightly higher than expected hospitalization rate for vertigo (dizziness) and migraine was reported (SHR 1.1-1.2). However, they were unrelated to time from first subscription. Hospitalizations for dementia were less frequent than in the entire population (SHR 0.7 for Alzheimer's disease, vascular dementia and other dementia). No increased rates were found for amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), multiple sclerosis or epilepsy. The findings do not indicate an excess risk of neurological disease due to mobile phone use. Shortcomings of the approach are due to selection bias with subscribers being mainly from higher socioeconomic strata and therefore lack of comparability with the national rates (lower risk of several diseases). Misclassification of exposure appears also likely with some non-users as subscribers and users not having a subscription with their own name.

In a Danish cohort study (Divan et al. 2009), maternal use of mobile phones during pregnancy was associated with a slightly, but significantly increased prevalence of behavioural problems at age seven years. A birth cohort of some 13,000 children born in 1997-1999 was established during pregnancy. At subsequent follow-up at age seven years, mothers were asked about their mobile phone use during pregnancy, as well as children's own mobile phone use at age 7 (participation 65%). Behavioural problems were assessed using a 25-item Strength and Difficulties Questionnaire, with rating of disorders related to hyperactivity, conduct, social relations etc. A quarter of the mothers reported mobile phone use during pregnancy and 30% of the children were using mobile phones. After adjustment for potential confounders (sex of the child, maternal smoking during pregnancy, socio-economic status and mother's history of psychiatric disease), prenatal exposure was associated with the overall problem score, as well as hyperactivity, conduct problems and peer problems (OR 1.2-1.5). Those children whose mother had been using a mobile phone during pregnancy and were using them themselves tended to have the highest odds ratios (OR 1.8; 95% CI 1.5-2.2). Four or more calls per day during pregnancy was associated with higher OR than less frequent use (OR 1.5; 95% CI 1.0-

2.2). The prevalence of behavioural problems reported in the study is comparable with the range seen in most previous studies (4-10% in school children). The instrument is suitable for assessing behavioural disorders in population studies, though not for diagnostic purposes. Though internally consistent, the results appear unexpected due to the very low exposure levels to the fetus. The authors themselves raise the possibility that some maternal behavioural patterns could be related to both mobile phone use and child's reported or true behavioural problems. However, the findings should clearly be assessed in other studies.

A cross-sectional study of 317 7th grade students aged approximately 13 years showed faster responses but less accuracy in learning and memory tasks associated with amount of mobile phone use (Abramson et al. 2009). The subjects were recruited from schools with participation of 66% and asked about their mobile phone use. Psychometric testing was carried out with CogHealth and Stroop colour-word test. The tasks included assessment of reaction time, simple and associative learning, working memory and movement monitoring. Age, gender, ethnicity, handedness and socioeconomic status were used as covariates. Three quarters of the children owned a mobile phone, made a median of eight calls and a similar number of SMS per week. Significantly shorter response times were associated with number of calls in one card and associative learning tasks. Correspondingly, lower accuracy was related to amount of mobile phone use in one-back, two-back and associative learning tasks. Similar results were found for number of SMS. Number of calls was also negatively associated with completion time of the Strip colour-word test. The researchers interpreted the findings as impulsive behaviour learned through mobile phone use.

In a cross-sectional questionnaire survey, frequency of self-reported health symptoms was associated with mobile phone use among 1269 Swedish adolescents (Söderqvist et al. 2008). The study design does not allow any conclusions about causality.

Reproductive studies

In a cross-sectional questionnaire survey in Norway (Møllerlokken et al, 2008), self-reported subfertility (failure to conceive within 12 months of intending pregnancy) was more common among men reporting work with telecommunication or radar (15-18% versus 9% among unexposed). The number of respondents was 2265, with participation proportion of 58%. Of the participants, 166 reported working with telecommunications and 99 with radar. The difference remained after adjustment for age, smoking, education and exercise. There was, however, no difference in the number of children or age at birth of the first child.

Another Norwegian cross-sectional study reported an association between exposure from radar, high-frequency aeriels and telecommunications equipment and self-reported subfertility among Navy personnel (Baste et al, 2008). Methods were similar to the above mentioned study. Of the 10,497 respondents, 22% reported working in the proximity of high-frequency aeriels. There was also a trend in risk of subfertility by amount of exposure to high-frequency aeriels, using a measure which appears to combine frequency and intensity of exposure. Radar and communication equipment were also evaluated but results were not reported.

A handful of studies have evaluated the effect of RF fields on sperm quality in humans. The rationale has been that testicular function is very sensitive to temperature elevation and such effect is produced by strong RF fields. However, the exposure to the testis under normal circumstances of mobile phone use appears very small. There is also substantial variability in the sperm quality parameters, which makes it more difficult to show an effect. Therefore, the causal nature of an association warrants closer scrutiny.

A recent study included 361 men attending an infertility clinic in 2004-2005 (Agarwal et al. 2008). Of the subjects, 11% did not use a mobile phone, of the rest roughly a third (roughly 100 men in each group) used it <2 , 2-4 and >4 hours per day. Men using tobacco or alcohol, as well as those with a history of orchitis, varicocele, or a chronic disease were excluded. Out of eight sperm quality indices, four were negatively correlated with daily call time in analysis of variance. The differences appear to show an exposure-effect gradient. The findings were unaltered when the men were divided into normospermic and oligospermic subjects and when cell phone use was dichotomised. The report is not entirely clear, which makes the interpretation of the results difficult. Subject selection or source of information concerning mobile phone use was not described and it appears that the effect of age was not taken into account.

The largest study to date was based on 371 men (Fejes et al. 2005). Those 39% with a clear etiology for fertility problems were excluded (organic testicular alterations, trauma, chronic disease, smoking or alcohol use). A weak positive correlation was found between proportion of sperm with slow motility and duration of mobile phone use ($r=0.12$). Correspondingly, a negative correlation was noted between duration of mobile phone use (months) and proportion of sperm with high motility ($r=-0.12$). Other semen quality indices did not show an association with duration. Sperm motility was also associated with daily call time. The results do not provide strong evidence for an effect of mobile phone use on sperm quality, because it appears that the effect of age was not controlled for. Other limitations of the statistical analysis include the use of Pearson correlation coefficient as the effect measure. It assumes normal distribution, which was not reported in the paper. Correlation may be strongly influenced by a few extreme observations. The statistical significance of the correlation coefficient is not sufficient indicator of an effect.

In addition, some reports with very small sample sizes (12-33 exposed men) have been published, but their results are not very informative (Weyandt et 1996, Schrader et al. 1998, Grajewski et al. 2000).

The evidence regarding effect of RF fields on sperm quality is weak and does not allow reliable evaluation of presence or absence of a health effect. Some suggestive positive results, though not very convincing, give justification for further studies with improved methods.

Transmitter studies

Studies on people living near transmitters have been reviewed by the IEG in 2003 and in 2006. No substantive conclusions could be drawn in any of those reports: "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” (IEGEMF 2003). “A study on symptoms near base stations did see an association between exposure level and prevalence of symptoms. These results need to be replicated and better understood before conclusions can be drawn” (IEGEMF 2006).

Some more information is available at present.

Cancer studies

All studies available at the time of the previous review were ecological studies, with no individual exposure assessment. Since then, two studies on childhood leukaemia in relation to environmental RF exposure have been published (Ha, et al. 2007; Merzenich, et al. 2008; Schuz, et al. 2008). The study from South Korea (Ha, et al. 2007; Schuz, et al. 2008) included 1,928 childhood leukaemia cases diagnosed between 1993 and 1999, and one hospital-based control per case. Additional information was provided by Schüz. Interestingly enough the Ha study did find some association with distance. Exposure assessment for each individual child was made through calculations of the RF fields generated by nearby AM radio transmitters. There was no association between childhood leukaemia and estimated RF fields; OR=0.83, 95% CI: 0.63-1.08 in the highest exposure quartile.

A study from Germany (Merzenich et al. 2008) included 1,959 childhood leukaemia cases diagnosed between 1984 and 2003 and 5,848 population-based controls. Individual exposure assessment was made through calculations of the RF exposure from AM and FM radio and television broadcast transmitters. An OR of 0.86 (95% CI: 0.67-1.11) was observed for the upper >95% quantiles compared to the <90% quantiles of the exposure distribution. Stratification of the analyses according to time period revealed no difference in the results before and after the introduction of mobile phones. These studies provide evidence against an association between RF exposure from broadcast transmitters and the risk of childhood leukaemia.

Other outcomes

In a small German study of 329 adults (18-65 years), RF exposure measured with a dosimeter was not correlated with reported symptoms (Thomas et al. 2008). Exposure assessment was based on a 24-hour measurement of field strength using the portable Maschek ESM-140 device recording readings every second. The frequency range covered GSM 900, GSM 1800, UMTS 2100, DECT and WLAN signals. Acute symptoms including headache, fatigue and concentration problems were recorded twice during the day (at noon and in the evening) and quantified on a four-point Likert scale. No consistent relation between exposure (divided into quartiles) and any of the symptoms was found. Limitations of the study include the small sample size (with little capacity to identify effects with up to three-fold increase in symptoms) and incapability of the measurement device to record while inert. The exposure levels were low (below 1% of the ICNIRP guideline).

A German cross-sectional study included approximately 30000 subjects (58% response rate). Distance to base station was measured through geo-coding, and categorized into >500 or ≤500 meters (Blettner, et al. 2009). A slightly higher prevalence of health

complaints was found among people living within 500 meters of a base station. People who were concerned about or attributed adverse health effects to exposure from mobile phone base stations reported a higher prevalence of health complaints.

The German study also included a component where RF exposure in the homes of a subset of participants were estimated through individual RF measurements of the background RF-EMFs from mobile phone base stations and other external sources (Berg-Beckhoff, et al. 2009). Measured exposure to RF fields from base stations was not associated with self-reported health or symptoms. A total of roughly 3500 subjects were recruited from the study participants of the previous cross-sectional study and measurements carried out in dwellings of 1500 subjects. RF field was assessed using the Antennessa portable dosimeter with four 4-minute spot measurements carried out in the homes of the participants. Exposure was categorized as below versus above detection threshold with the highest decile as the high-exposure group. Four validated questionnaire instruments were used for assessing sleep quality (Pittsburgh Sleep Quality Index), headache severity (Headache Impact Test), stress (Von Zerssen list) and health-related quality of life (SF-36). None of the symptom scores was associated with the measured field strength. However, persons who were concerned about or attributed adverse health effects to base stations had higher sleep problem and stress scores. The cross-sectional setting does not allow evaluation of cause and effect relations.

Conclusions on transmitters

Generally, studies of symptoms and well-being find a higher prevalence of symptoms and less well-being among persons who are concerned about exposure from base-stations, whereas there is little evidence for an association between measured RF levels and the studied outcomes.

Interphone methods

Several publications from the Interphone group examined potential recall and selection biases as well as modelled distribution of RF energy in the brain. In addition, several publications discussed methodological issues as they apply to Interphone.

To investigate potential recall bias, and whether it differed between cases and controls investigators from Interphone centres in Canada, Australia, and Italy compared traffic/billing records to recalled mobile phone use (Vrijheid et al. 2009a). The comparison was based on about 1/4 of cases (N= 212) and controls (N= 296) in these three countries, who did not share the phone with others more than 25% of the time. In addition to the usual computer-assisted interview about past phone use, investigators obtained network operator data from the date available or start of subscription, whichever was latest, until date of interview or end of the subscription, whichever was earliest. In Canada one operator could not provide records for 40% of subjects and, in Australia, operators provided data on outgoing calls only. To correct for the missing incoming calls, outgoing calls were doubled. Operator data could be retrieved approximately four years back in time. Subjects in the validation study did not differ greatly from the full analysis population by age, sex, time since start of phone use, or lifetime cumulative phone use. For about 40% of cases and controls there was complete agreement between categories of self-reported and operator-recorded number and duration of calls. For another 30-40 %

of both cases and controls results fell into adjacent categories. There was moderate agreement between reported and actual phone use with weighted kappa-values of 0.45 for most of comparisons. Both cases and controls underestimated the number of calls they made by a factor of 0.8, but overestimated call duration by a factor of 1.4. For cases, but not for controls the overestimation increased with increasing time before interview. Accuracy of lifetime use and time since start of use differed by amount of use, with under-reporting among low users and more over-reporting for higher use categories. The potential differential exposure misclassification in studies using self-reported phone use, especially for more distant time periods, may cause positive bias in estimates of disease risk. Network operator information is presumably more accurate and objective, but may be lacking in validity: some networks only have information about outgoing calls and the information they have refers to subscriptions rather than actual users. Neither self-report nor records provide all the relevant or completely accurate data. Thus all studies based on phone use are affected by exposure misclassification, which if non-differential could dilute risk estimates.

In several of the Interphone studies, there were indications that non-participation was related to exposure status, with mobile phone users more willing to participate than non-users. To evaluate the potential magnitude of selection bias, most of the study centers of Interphone sought a short interview with non-participants (Vrijheid et al, 2009b). They were able to elicit responses from 57% of control refusers and 41% of case refusers. In all centers, a lower rate of regular mobile phone use was found in controls who refused the full interview (56% overall) compared with controls who were full participants (69%), regardless of whether the study was presented as a “mobile phone” study or not. The same pattern was found for cases: 50% of case refusers were regular mobile phone users, compared with 66% among full participants. Assuming that complete non-respondents were similar to partial respondents, selection bias introduced by non-participation was estimated to cause a downward bias of around 10% in odds ratios for regular mobile phone use. It is not known if such a bias would be present differentially between different categories of users e.g. among regular versus infrequent users.

Even if accurate information on use was available inferring radiofrequency radiation exposure from data on mobile phone use is difficult. Some of the Interphone investigators estimated the distribution of RF energy in anatomical structures of the brain from 110 different mobile phone models in use in Europe and Japan (Cardis et al, 2008). Measurements were made in France and Japan on 76 phones operating in the 800-900-MHz band (either PDC or CDMAOne systems) or the 1500-MHz PDC band and on 34 GSM phones operating in the 900- and 1800-MHz bands. The SAR data were obtained using a phantom of the head filled with a homogeneous liquid. Measurements of the electric field were taken at the centre of each cm^3 cube within the phantom with the phone operating at full power. It appears that most of the energy (97-99%) is absorbed in the brain hemisphere on the side where the phone is used, mainly (50-60%) in the temporal lobe on the side of the phone use. Analyses by marketing year and type of antenna did not show large variation. Sources of uncertainty include the use of a heterogeneous phantom, human anatomical variability, localization of the anatomical structures, and the interpolation and extrapolation methods used to derive the SAR distribution. Nevertheless, results appear to be fairly robust with the highest SAR in the

temporal lobe despite the changes in the type and size of the phones and position of the antenna.

Methodological considerations in epidemiological studies of mobile phone use

Exposure misclassification

Exposure assessment in most epidemiological studies of mobile phone use and cancer has been based on self-reported information on duration and amount of mobile phone use from interviews or postal questionnaires. A few studies have used information recorded by network operators for billing purposes. When information is obtained directly from the participants, more detailed data can be collected. However, self-reported data may be subject to recall and reporting bias. Call information from mobile phone operators is presumably more accurate and objective, but may be lacking in validity: some operators only have information about outgoing calls and the information they have refers to subscriptions rather than actual users. Often, operator data are unable to identify corporate users.

All studies based on phone use are affected by exposure misclassification. As discussed above, validation studies have shown that both healthy individuals and brain tumour patients have a tendency to overestimate the length of their calls and to underestimate the frequency (Vrijheid, et al. 2009a; Vrijheid, et al. 2006), and that heavy users tend to overestimate, whereas light users underestimate their use. In addition, the overestimation by patients increased the longer back in time the mobile phone use referred to (Vrijheid, et al. 2009a), which was not seen among controls. It is likely that non-differential exposure misclassification is present in available studies, which could dilute risk estimates, should there be a true effect. If there is no true association between the exposure and the disease, however, non-differential exposure misclassification will not affect the risk estimates, i.e. risk estimates will be close to unity anyway. The differential recall among cases and controls (recall bias), i.e. the tendency for cases to overestimate exposure for more distant time periods, would lead to a positive bias, which could even result in spurious associations. The validation study investigated recall over a period of approximately four years (Vrijheid, et al. 2009a); there are currently no data available on quality of recall for more distant time periods. There is also a lack of data on recall of time since first mobile phone use.

Use of network operator information avoids the problem with recall bias, but there may be substantial non-differential exposure misclassification, e.g. corporate mobile phone users are categorized as unexposed, some subscribers may not use the phone themselves but own a subscription used by somebody else. The magnitude of the bias caused by non-differential exposure misclassification depends on the prevalence of the exposure. If the exposure in the population is rare, as for example “having used a mobile phone more than 10 years”, exposure misclassification is unlikely to have a substantial effect on risk estimates among long-term mobile phone users, even if corporate users are classified as unexposed.

Laterality analyses

RF exposure during mobile phone use is highly localized and penetrates only a few centimetres into the brain. Therefore, mobile phone use on one side of the head is not expected to affect tumour risk on the other side. In some case-control studies questions have been asked about the habitual side of mobile phone use, and separate analyses have been made of the association between tumour risk and mobile phone use on the same (ipsilateral) and opposite (contralateral) side of the head. There are currently no validation studies of the retrospective self-reported side of use, and there is no evidence of consistency over time in the preferred side of use. Retrospective self-report of preferred side of use may be subject to bias. If cases believe that mobile phone use may have caused their tumour, they might overreport mobile phone use on the same side as the tumour. Should there be a causal association between mobile phone use and brain tumour risk one would expect an increased risk on the same side of the head as the phone is held, and a null finding on the opposite side. On the other hand, if some brain tumour patients believe that mobile phone use have caused their tumour, and overreport use on the affected side, this would result in an apparent risk increase on the same side of the head accompanied with a decreased risk on the opposite side. There is indeed evidence of such a pattern in most of the available studies (Ahlbom, et al. 2009; Schuz 2009). In the large Nordic-UK study of mobile phone use and glioma a 40% risk increase was seen for ipsilateral use that started at least 10 years prior to diagnosis. A null-finding was found for contralateral use. This result received considerable attention, as it was in agreement with what would be expected if the association was causal. However, a closer look at the full pattern of the results calls for a cautious interpretation. The overall result for >10 years since first use was 0.95 (95% CI 0.74-1.23); for ipsilateral use 1.39 (95% CI 1.01-1.92) and for contralateral use 0.98 (0.71-1.37), i.e. both the ipsilateral and the contralateral results are higher than the overall risk estimate. There must be a considerably reduced risk for a third group of subjects, i.e. those who did not report side of use, or had a centrally localized tumour (Schuz 2009). Furthermore, the ratio of ipsi- to contralateral ORs is similar over all categories of time since first use, also for a very short duration of use, i.e. starting less than five years prior to diagnosis, which is not what one would expect if the association is causal. Thus, there is strong evidence that the laterality analyses are influenced by recall bias. Please refer to Schuz 2009 for a thorough discussion of the complexity of laterality analyses.

To avoid recall bias and limit non-differential exposure misclassification, prospective studies are needed where self-reported information on mobile phone use and laterality are obtained prior to disease occurrence and are combined with information from network operators. Special methods might be required for children as they might not have linkable operator records. Studies of rare outcomes, however, require very large study populations or very long follow-up periods.

Apparently reduced risks

Many epidemiological studies of mobile phone use and brain tumour risk observe effect estimates below unity in analyses of mobile phone use and brain tumour risk, especially for short term mobile phone use, which if true would imply a protective effect. Reduced risk estimates were seen in a number of case-control studies, from the early US studies to

the more recent Interphone studies, and also in the Danish cohort study. Some possible explanations for the apparently reduced risks are discussed below.

Selection bias

A case-control study relying on self-reported mobile phone use is dependent on the willingness of cases and controls to participate in the study. There has been a general tendency of decreasing participation rates world-wide during the past decade. Generally, cases are more willing to participate as they are often more interested in research aiming at finding causes to their disease. If willingness to participate is related both to the disease and to the studied exposure selection bias might be introduced by non-participation. In the Interphone study participation rates varied considerably between study centres, and a non-responder questionnaire was used to assess the impact of non-participation on risk estimates, as described above. Both among cases and controls, mobile phone users were more willing to participate, and with lower participation rates among controls. It was estimated that selection bias would push risk estimates downward approximately 10%, which explains some, but not all of the risk reduction.

Prodromal symptoms

Apparently reduced risks were seen in many of the case-control studies, from the earliest studies of mobile phone use conducted in the US to the most recent studies performed within the Interphone collaboration. It is interesting to note that a reduced risk was seen also in the Danish cohort study (Schuz et al. 2006), which is registry based and therefore not affected by selection bias. The time period during which all the epidemiological studies have been performed is characterized by a rapidly increasing prevalence of mobile phone use in the population; from less than 10% in the beginning of the 1990s to almost 100% in 2005. The steepest increase was seen in the late 1990s and early 2000s. There is a possibility that brain tumour patients, because of prodromal symptoms, might have been less likely to take on a new technology during the last few years prior to their tumour being discovered and diagnosed. If the exposure prevalence (mobile phone use) is increasing rapidly in the rest of the population, the proportion of mobile phone users would be lower among brain tumour patients compared to the general population, because the cases are less likely to adopt mobile phone use, resulting in reversed causality. Some might argue that glioma is a rapidly growing tumour that manifests itself in a short period of time, and therefore it would be sufficient to disregard the year prior to diagnosis when assessing exposure, as most studies have done. However, there is evidence of prodromal symptoms being present several years prior to glioma diagnosis in a study of the association between epilepsy and brain tumours (Schwartzbaum, et al. 2005). Epilepsy was more prevalent among both low-grade and high-grade glioma cases, also more than 8 years prior to glioma diagnosis. An association was seen also for meningioma, but considerably weaker. If exposure occurring after the disease onset counts toward exposure, bias may be introduced in the study, as the disease itself might affect the likelihood that a person becomes exposed or the amount of exposure. If persons with a brain tumour, who have not yet been diagnosed, are affected by their disease in a way that makes them less likely to start to use a mobile phone in the period preceding diagnosis, the risk estimate for short term mobile phone use will appear to be reduced.

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