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Recent Research on Mobile Telephony and Cancer and Other Selected Biological Effects: First annual report from SSI's Independent Expert Group on Electromagnetic Fields.

SSI's Independent Expert Group on Electromagnetic Fields, 2003

Preface

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

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

Prof. Anders Ahlbom, Karolinska Institutet, Stockholm, Sweden (chairman);

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

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

Dr. Harri Vainio, IARC, Lyon, France (currently Occupational Health Institute, Helsinki, Finland);

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

Dr. Eduard David, University of Witten/Herdecke, Witten, Germany;

Prof. J. Malcolm Harrington, London, UK.

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

Stockholm in December 2003

Anders Ahlbom
Chairman

Executive summary

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

Tumours in mobile phone users

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

Tumours in people living near transmitters

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

Carcinogenicity

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

Heat shock proteins

In recent years several articles have described effects of radiofrequency signals on the expression of stress proteins (heat shock proteins, HSP) *in vitro* and *in vivo*. These HSP act to prevent or repair protein alteration due to stress. These observations were done at low exposure level and a direct effect of temperature elevation can be excluded. There are many confirmation studies in progress and it is presently not possible to conclude about the existence and the mechanism of these effects and even less about relevant health consequences. However, this is an important area for research as HSP expression might be used as a marker of RF exposure.

[1] Stewart report

Blood brain barrier

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

Precautionary framework

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

Conclusion

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

Introduction

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

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

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

Tumours in mobile phone users

Brain tumours

To date, only a small number of epidemiological studies on mobile phone use and cancer risk exist; the majority of these studies focus on brain tumour and acoustic neuroma (Table 1 and 2) but some study other tumour types (Table 3).

The first case-control study of brain tumours was conducted in Sweden (reported in three publications: Hardell et al. 1999; 2000; 2001), and included cases diagnosed in two regions in Sweden and still alive when recruited to the study, and two controls per case matched for sex, age, and regional population register (Table 1). Details of mobile phone use were gathered by self-completed postal questionnaires complemented by a telephone interview (Hardell et al. 1999). High participation rates were reported in the publication, but in fact only about one third of the total number of malignant brain tumour cases in the population was included (Ahlbom & Feychting 1999), probably because many cases had died before they were approached by the investigators. The response rate in controls was remarkably high for a population based study. There was no overall association of phone use

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

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

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

A Danish cohort study (Johansen et al. 2001) included 420,095 cellular network subscribers (80% of all private subscribers in Denmark), 31% of whom had begun subscriptions in 1993 or earlier. The cohort constituted approximately 10% of the adult Danish population, and was followed from first subscription through 1996. Cancer incidence in the cohort was ascertained by linkage to the Danish Cancer Registry with average follow-up for analogue and digital subscribers being 3.5 and 1.9 years respectively. Standardised incidence ratios comparing cancer incidence in phone users (mostly digital) with national rates allowing for sex, age and period, showed reduced risk of cancer overall (SIR = 0.89, 95% CI: 0.86 – 0.92), and of brain and nervous system tumours (SIR= 0.95, 95% CI: 0.81 – 1.21). Risks did not vary by time since first subscription, age at first subscription, use of analogue versus digital telephones, duration of digital phone use, anatomical location or histology of brain tumours. Acoustic neuroma was not analysed separately. The study has

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

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

A second Swedish case-control study was conducted by Hardell et al. (reported in three publications: 2002a, 2002b, 2003), including cases of brain tumour ascertained 1997 - 2000, and alive at the time of recruitment to the study. One control per case, matched for age, sex and region, was selected from population registers. Information on exposure to cellular and cordless phones was collected through mailed questionnaires and completed over the phone, similarly to the first study. Excluding cases with erroneous diagnoses (e.g. metastasis or wrong diagnosis date) left 2253 available cases of which 1303 were included in the study (58%). Results for all brain tumour types combined are driven by the acoustic neuroma results; no associations were found between mobile phone use and malignant brain tumours, or benign brain tumours other than acoustic neuroma. An increased risk of 3.5 (95% CI: 1.8-6.8) was found for acoustic neuroma among users of analogue mobile phones, whereas results for digital phones were close to unity. For other tumours located in the temporal lobe (where

all acoustic neuromas are located) an increased risk of meningioma was indicated among users of analogue phones. However, the highest risk seems to be for meningioma cases with a short latency of mobile phone use (within 5 years). Sub-analyses with different latent periods showed no coherent patterns for any tumour types. There were no adjustments for confounding variables beyond adjustment for use of other types of mobile phones, and matching variables. The study has a limited power to study effects of long-term use of digital phones. It is noteworthy that the prevalence of mobile phone use had not increased much between the first and second Swedish study; the increase in the proportion of users among controls was at the most 6%. Between 1996 and 2000 mobile phone use in the general Swedish population increased from 28% to 71%. These estimates are based on number of subscriptions in the total Swedish population, and may be an overestimate because some persons have multiple subscriptions. However, multiple subscriptions cannot account for the entire difference in the increase in proportion of users. As in the first Swedish study (Hardell et al. 1999), the long delay between diagnosis and case recruitment tend to lead to loss of high-grade tumours.

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

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

Other tumours

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

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

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

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

Discussion and conclusions

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

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

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

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

Tumours in people living near transmitters

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

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

Since the Stewart report, we are only aware of one other study on cancer to have been published in the scientific literature and that is a study based on the population leaving near the Vatican Radio Station (Michelozzi et al. 2002). The Vatican Radio station is a very powerful station that transmits all over the world and people living in the neighbourhood have been concerned about possible health effects and have demanded an epidemiologic investigation in the population residing around the transmitters. The station consists of numerous transmitters with transmission powers ranging from 5 to 600 kW, and different frequency bands (nine transmitters for short waves with frequencies of 4,500-21,850 kHz, and three transmitters for medium waves, with frequencies of 527-1,611 kHz). This study looked at leukaemia mortality in adults and leukaemia incidence in children in the population living within a 10 km radius circle of the centre of the transmitters. The authors divided the circle in 2 km wide bands to allow for trend analyses using Stone's test for decreasing rates with increasing distance. In adults and with both genders taken together the SMR within 2 km was 1.8 (95% CI: 0.3-5.5) based on 2 cases. Stone's test gave a p-value of 0.14. The excess risk and the trend were essentially confined to males. In children the SMR for those living within the 2 km radius circle was 6.1 (95% CI: 0.4-27.5) based on one case. Elevated SMRs were observed for all cumulative bands up to 10 km but all had wide confidence intervals and the total number of cases within the 10 km radius circle was 8. The Stone test for trend was reported as p=0.004. No systematic EMF measurements were made in the area and the epidemiologic analyses were based on the assumption that distance from the sources can serve as a proxy for exposure. The numbers of cases were small in particular for children, which precludes firm conclusions. For adults, the results are somewhat inconsistent in that the risk elevations are mainly confined to males.

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

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

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

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

Cancer-related in vivo and in vitro studies

Carcinogenicity in animals

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

RF exposure alone, without exposures to known carcinogens

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

La Regina et al. (2003) performed a two-year carcinogenicity study using F344 rats. Eighty female and 80 male rats per group were exposed to one of two mobile phone signals (FDMA or CDMA) or sham-exposed. The rats were exposed 4 h/d, 5 days per week, and the brain

SAR was 1.3 W/kg. No significant differences were found between the exposed and sham-exposed animals for any tumour in any organ.

RF exposure combined with known carcinogens

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

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

Heikkinen et al. (2001) used ionising radiation as an initiator and tested mobile-phone type 900 MHz radiation as a possible promoter. Female CBA/S mice, 50 animals per group, were exposed to ionising radiation in the beginning of the study and then to RF radiation for 1.5 h per day, 5 days a week for 78 weeks. One group was exposed to a continuous NMT-type RF field at a whole-body average SAR of 1.5 W/kg and another group to a pulse-modulated GSM-type field at 0.35 W/kg. The carcinogenic action of ionising radiation was at the desired moderate level - clear and statistically significant, but not too strong so that it would have masked any promoting effects. For example, lymphoma was observed in 24% of the animals exposed to ionising radiation, compared to no lymphomas found in the control animals. RF exposures did not cause significant further increase of lymphoma or any neoplastic lesion. The incidence of all primary malignant neoplasms pooled was slightly higher in the RF-exposed animals, but the difference from animals exposed only to ionising radiation was not statistically significant. Overall, the results of this study did not provide evidence for cancer promotion by RF radiation.

Two recent studies have investigated possible promoting effects of mobile-phone type RF radiation on rat mammary tumours initiated by 7,12-dimethylbenz(a)anthracene (DMBA). Bartsch et al. (2001) conducted three independent experiments on Sprague-Dawley rats exposed to an initial dose of DMBA and continuously to GSM-modulated 900 MHz RF fields. The whole-body average SAR was 17.5-70 mW/kg. In the first experiment, median time to the development of the first malignant tumour in each animal was significantly longer in the exposed group than in the sham-exposed group. However, this finding was not confirmed in the two later experiments with the same protocol. Overall, the study did not demonstrate any significant differences between the groups in tumour latency or incidence. The same experimental model (Sprague-Dawley rats and DMBA) was used by Anane et al. (2003), but the exposure levels were higher, and the animals were exposed only 2 h/d, 5 days per week. The RF field exposures started 10 days after the DMBA treatment. In the first of two independent experiments, 16 rats were sham-exposed and three groups of 16 rats were

exposed to whole-body average SARs of 3.5, 2.2 or 1.4 W/kg. In the second experiment, the SAR levels were 1.4, 0.7 and 0.1 W/kg. In the first experiment, the development of tumours was statistically significantly accelerated at 1.4 and 2.2 W/kg but not at 3.5 W/kg compared to the sham-exposed group. In the second experiment, there were no differences in tumour appearance between the two lower exposure levels and the sham-exposed group, but tumours appeared significantly later in the 1.4 W/kg group. Multiplicity of tumours was not significantly increased by the exposures (in the second experiment, the number of tumours per tumour-bearing animal was significantly decreased at 1.4 W/kg). Overall, there were no consistent effects on latency, incidence, multiplicity or tumour volume. Other studies using the DMBA-induced mammary tumour model are ongoing.

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

Genotoxic effects

The association between cancer and genotoxicity is well known. For example, the carcinogenic effects of ionising radiation, UV radiation and many chemical carcinogens is based on their ability to cause DNA damage and consequent gene mutations. Genotoxicity of RF radiation has been tested in many studies both in animals and *in vitro*. Some of these studies have evaluated also possible combined effects with known DNA-damaging agents. Concerning studies published before 2000, the Stewart report concluded: *"Several different assays of genotoxicity have failed to produce clear evidence that RF radiation is genotoxic at non-thermal levels. The most consistent results come from micronucleus formation, but these are not simple to interpret and have uncertain implications for health."* Four studies published after the Stewart report found no effects on DNA damage, chromosomal aberrations or micronuclei in human peripheral blood lymphocytes or in rat peripheral blood or bone marrow cells exposed to two mobile phone signals (CDMA at 847.74 MHz , FDMA at 835.62 MHz) or to 2.45 GHz microwaves (Vijayalaxmi et al., 2000; Vijayalaxmi et al., 2001c; Vijayalaxmi et al., 2001a; Vijayalaxmi et al., 2001b). Two recent studies are reviewed below.

Tice et al. (2002) exposed human blood cells to RF fields using analog or two different digital (CDMA, TDMA) mobile phone signals at 837 MHz, or a digital (GSM) phone signal at 1909.8 MHz. The cells were exposed for 3 or 24 h at specific absorption rates of 1.0-10.0 W/kg. The temperature of the cultures was kept at 37–C by controlling the temperature of the exposure chamber. DNA damage was evaluated in leukocytes using the alkaline single cell electrophoresis ("comet") assay. Chromosomal damage was assessed in lymphocytes mitogenically stimulated to divide post exposure using the cytochalasin B-binucleate cell micronucleus assay. No increased DNA damage was observed in the comet assays. Micronuclei were not increased in leukocytes exposed for 3 hours, but exposure for 24 h at 5 or 10 W/kg resulted in a significant increase in the frequency of micronucleated lymphocytes.

The magnitude of the effect was about 4-fold, and all four signals produced a similar response. This is a well-conducted study, and the results appear to be reproducible within the same laboratory. The biological relevance of the positive micronucleus finding is uncertain. Micronuclei can originate either from chromosome fragments (indicating damage to DNA) or from loss of whole chromosomes. Differentiation between these two mechanisms (by using a centromere-specific probe) was not done in this study. The effect was observed at relatively high SAR, and a thermal mechanism remains a possible explanation for the increased micronuclei. There is no obvious explanation for the difference between these results and those of Vijayalaxmi et al. (2001a,b), who found no increase of micronuclei in human lymphocytes using similar methods and similar mobile phone signals at maximum levels of 5 or 5.5 W/kg. Inaccuracies in dosimetry might explain the difference, if there is a threshold for this effect near 5 W/kg.

Mashevich et al. (2003) exposed human peripheral lymphocytes to continuous wave 830 MHz RF fields. The cells were exposed for 72 h using specific absorption rates of 1.6-8.8 W/kg. Heating by the RF fields was compensated by lowering the incubator temperature. Aneuploidy (loss or gain of chromosomes) was assessed by using a fluorescence in situ hybridization probe for detecting the centromere of chromosome 17. An increase of chromosome 17 aneuploidy was observed as a function of increasing exposure levels. The increase was about 100% at 8 W/kg, whereas no increase was seen at 2 W/kg. The effect was statistically significant at levels exceeding approximately 3 W/kg. The increased aneuploidy was accompanied by increased frequency of asynchronous replication of repetitive DNA arrays associated with the centromere – the same research group has previously reported that such changes are associated with aneuploidy and cancer. In separate additional experiments, aneuploidy was not found to increase with increasing temperature between 34.5–C and 38.5–C. Temperatures of 40-41–C produced an 80% increase of aneuploidy. Because the average temperature of the medium never exceeded 38–C during RF exposure, the authors concluded that the RF effect was nonthermal. The biological implications of the findings are not clear. While aneuploidy seems to be associated with cancer and genomic instability (Duesberg et al., 2000), its causal role in carcinogenesis is controversial.

Non-genotoxic cancer-related effects

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

Effects on cell proliferation

There is no doubt that increased cell proliferation is important for the process of carcinogenesis, and many known tumour promoters are able to stimulate cell proliferation. According to the Stewart report, studies published before 2000 “*do not demonstrate convincing, consistent changes in cell proliferation under conditions that mimic emissions from mobile phones or base stations.*” No studies published after 2000 were identified. The Stewart report also reviewed studies on ornithine decarboxylase (ODC) activity *in vitro*. ODC is a key enzyme in the synthesis of polyamines. Its activity is elevated in rapidly growing cells (e.g., cancer cells), and it can be considered a marker of cell proliferation. Several known tumour promoters increase ODC activity. The Stewart report concluded: “*Pulse-modulated RF fields from mobile phones may cause a slight increase in ODC levels and activity, at non-*

thermal levels. However, it is very unlikely that these small changes could…have a tumour-promoting effect." Desta et al. (2003) exposed murine L929 fibroblasts to a 835 MHz TDMA-modulated RF field at SARs from <1 W/kg to 15 W/kg. No statistically significant differences between exposed and sham-exposed cells were found at low SAR values. At SARs high enough to cause measurable heating, a dose-dependent decrease of ODC activity was observed. Heating without RF radiation caused a similar decrease. Thus, this study did not confirm the previously reported RF-field-induced increase of ODC activity *in vitro*. Two recent studies have evaluated ODC or polyamine levels *in vivo*. Stagg et al. (2001) did not find effects on ODC activity, in brain tissue of rats after acute exposure (2 hours) to pulsed 1.6 GHz field (Iridium signal) at 0.16, 1.6 or 5 W/kg. In the carcinogenicity study described above (Heikkinen et al., 2003) no changes were observed in skin polyamine levels after chronic exposure (2 years) of mice.

Effects on apoptosis

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

Neoplastic transformation *in vitro*

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

Conclusions

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

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

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

Heat shock proteins and mobile telephony

The Stewart report discussed studies on gene expression from the perspective of cellular stress response, and concluded: *"While there is currently little evidence that exposure to mobile phone radiation causes a stress response in mammalian cells, judged by elevated gene expression, the results on nematode worms are indicative of non-thermal influence on gene expression."* They referred to the findings on de Pomerai and colleagues, who found increased expression of a heat shock gene in worms exposed to low levels of RF fields [de Pomerai et al., 2000].
Since then, several articles have been published on the potential effects of mobile telephony microwaves on processes involving heat shock proteins (HSP). This is a rather new area of research within bioelectromagnetics. Various stress factors such as excess temperature cause alterations of protein conformation (unfolding, denaturation or aggregation). Since the biological function of a protein is highly dependent upon its structure, stress affects the function of proteins. The HSP are acting as chaperones to facilitate the refolding of altered proteins. They also have a function at key regulatory points in the control of apoptosis (programmed cell death) and chaperones have thus been implicated in the control of cell growth. Discovered in 1962, HSP are classified mainly on the basis of their size (HSP 110, 90, 70 and small HSP). For example, HSP 110 and 70 confer heat resistance to the cell by preventing aggregation and maintaining the folded structure. Elevated levels of HSP are thus indicators of the presence of stress. This is why they have been monitored as potential markers of RF exposure.

In vivo studies

An early and transitory induction of hsp27 ARNm had been observed in the brain of rats locally exposed to RF (900 MHz, CW, 4-hour exposure) with a SAR threshold of 7.5 W/kg (Fritze et al., 1997a).
As stated above, the group of de Pomerai in England published a short article describing results obtained on small worms called nematodes (*Caenorhabditis elegans*) exposed to low-level microwaves (de Pomerai et al., 2000). The endpoint of the assay was the indirect detection of hsp expressed following exposure. The authors had developed transgenic nematodes in order to follow the production of hsp16. In terms of hsp expression, the transgenic worms behaved as if they had been heated by 3°C with respect to controls, and this could not be accounted for by microwave exposure at a low level (ca. 10^{-3} W/kg). Further investigation by the same group led to the publication of results on the growth and maturation of the nematodes (de Pomerai et al., 2002): they observed identical hsp16 increases in the larvae of worms exposed at 10^{-3} W/kg during 20 hours at 25°C and in sham-exposed larvae maintained at 28°C. Moreover, growth of exposed larvae was 18% faster than that of shams and maturation towards the adult stage increased by 28-40%. These two biological parameters decreased when larvae were kept at 28°C. According to the authors, these observations bring evidence of a nonthermal effect of the microwaves. Further work done *in vitro* by the same authors addressed the mechanism of the observed effects (see below). Replication studies of the data of the de Pomerai group by other research teams are likely to be undertaken soon.

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

In vitro

An increase in expression and phosphorylation of the Hsp27 protein in human endothelial cells[3] (GSM-900, 2 W/kg, 1-hour exposure) was published by Leszczynski et al. (2002).
In Australia, Laurence et al. (2000) studied the effects of pulsed microwaves on the induction of HSP70 response in murine cells. Short bursts of 2450-MHz microwaves induced an increase of HSP70 with the dose (12-58 W/kg). The authors made some theoretical hypotheses based on these data (see below).

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

[3] EA.hy926 cell line

Mechanisms

Laurence et al. (2000) did some theoretical modelling to address the mechanistic issue related to their biological observation (see above). They estimated a cooling time constant of one nanosecond for a 10-nm diameter protein absorbing the microwaves, while protein unfolding occurs on a 50-nanosecond time scale. A hypothesis of theirs is that the power "window" phenomenon, in which biological effects are observed at various low power levels, may be caused by an incomplete triggering of the heat shock response. Little evidence is given by the authors to support such a mechanism.
Recently, De Pomerai et al. (2003) have performed some interesting experiments and made some hypotheses. They showed that exposure to low-level microwave radiation (15-20 mW/kg) enhanced the aggregation of bovine serum albumin in vitro in a time- and temperature-dependent manner. It also promoted amyloid fibril formation by bovine insulin at 60°C. They also showed that heat-shock responses were suppressed using RNA interference. They concluded that HSP response to microwaves is probably triggered by conformational alteration to cellular proteins.

Conclusion

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

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

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

Studies on the blood-brain-barrier

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

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

permeability of the BBB immediately after exposure even at low exposure level (Salford et al. 1994, Persson et al. 1997).

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

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

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

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

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

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

Meanwhile, the Hossmann group in Germany who had found a minor effect at high SAR (around 7.5 W/kg) (Fritze et al. 1997) concluded recently that the neuropathological relevance of an increased BBB permeability is low because even the most pronounced alterations induced by microwave exposure are small compared to established models of BBB disturbances and because BBB changes are quickly reversed (Hossman & Hermann 2003).

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

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

Precautionary framework

Definitions and Goals

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

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

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

The Hierarchy of Responses

Precautionary actions that are proportional to the degree of scientific uncertainty, the severity of possible harm, the size and nature of the affected population, and the cost of the proposed actions should be taken to protect public health. There is a hierarchy of responses, depending

on the extent of the anticipated harm. Often, of course, the anticipated harm cannot be specified, and ranges of outcomes are all that can be predicted.

Where the evidence of danger is weak, regulation should usually be avoided, but proportional precautionary measures might still be justified, e.g. personal choice to use a hands-free device. In such cases, continuing research is appropriate to fill gaps in existing knowledge and to ensure that the danger is not larger than current understanding suggests. If the evidence of harm is suggestive, government might disclose the risk to the public or require product labelling; communication and engagement programmes can be used to assist people to understand the issues and to make their own choices about what to do. In the face of plausible evidence of significant harm, consideration should be given to mitigation and regulatory controls to reduce or to eliminate that harm. Where the evidence of likely harm is strong, limiting exposure and general bans should be considered, certainly if the bans do not create substitute risks or impose costs that exceed likely benefits. In all cases, precautionary measures should be proportional to existing knowledge of the risks.

Evaluating Benefits and Costs

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

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

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

Conclusions

This first annual report of SSI's independent expert group looks at studies on possible biological effects of radio frequency electromagnetic fields. The focus is on epidemiological and experimental cancer research and on blood-brain barrier damage and heat shock proteins. In none of these areas has there been break through results that have warranted firm conclusions in one way or the other. Indeed, while quite a number of new studies have been published within these areas in recent years, the overall scientific assessment has not changed markedly since the Stewart report was published and the conclusions that were formulated at that time are still to a great extent valid. It is worth noting, however, that intense research is currently ongoing in several countries. This research is often part of a scientific program that

has been aimed to fill the gaps in knowledge identified by the WHO EMF Project in order for the WHO to complete its assessment of health risks and electromagnetic fields. Given the complexity of the research area it is essential that both positive and negative results be replicated before accepted. Given the increase of new technologies, it is essential to follow various possible health effects from the very beginning, particularly since such effects may be detected only after a long duration, due to the prolonged latency period of many chronic diseases. Thus, more research is needed to address long-term exposure, as well as diseases other than those included in the ongoing case-control studies.

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