German Mobile Telecommunication Research Programme
International Workshop on Long term effects
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Rapporteur's Report

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Welcome address: W. Weiss, Federal Office for Radiation Protection

Welcome to this fifth workshop of our German research program on the effects of high frequency electromagnetic fields. This workshop deals with long term effects and is the fifth of the series of workshops that we have organized so far. In discussions tomorrow we will address these general aspects: what was the situation before we began the program, what has been achieved by the various projects, where are the lessons learned when we will have finished the whole project? Where are there gaps, and can we define minimum standards for future work? Are there any results that may have an impact on guidelines for standard setting?

A. Böttger, Federal Ministry for the Environment, Nature Conservation and Nuclear Safety

In the late 1990s we had intense discussion in Germany about possible health effects of mobile telecommunication systems. To make the discussions more objective, the Federal government asked the Radiation Protection Commission (RPC) to prepare an evaluation on the knowledge of health effects which may occur below the safety standards and, in 2001, the RPC completed the recommendation on limit values and precautionary measures for the protection of general public against electromagnetic fields. One of the major recommendations of RPC was for additional research to address open questions about possible health effects of EM fields. In December 2001, the mobile telephone network providers agreed to support a research program under the Federal Ministry of Environment and provided 8.5 million Euros in additional to funds provided by the government. This program, the German Telecommunications Research Programme, consequently had a total budget of 17 million Euros for research. It was organized and coordinated by the Federal Office of Radiation Protection on behalf of the Ministry of Environment. It comprised at least 50 projects, which were chosen to cover the whole field of possible health effects. This is the fifth and final workshop to discuss the results of this program, which is now drawing to a close. All of you are invited to attend an international conference in Berlin in June 17-18 (2008) to discuss the results of the program, draw conclusions, and discuss inter-connections with results of other research programs. This program is a big step forward to providing a much more solid risk assessment, and will be used by the German Government in deciding how to change national regulations in this sphere.

Session 1 : Blood Brain Barrier

Chair: D. Begley, Centre for Neuroscience Research, Kings College London

1-1

In vitro experiments on exposure to RF-fields of mobile telecommunication.

H. Franke, University Hospital Münster, Dept. of Neurology, 48129 Münster, Germany;

The study examined changes in gene expression following RF-EMF exposure using an in vitro model for the blood brain barrier. The goal was to identify potential molecular targets and pathways affected by exposure to RF radiation. Primary cultures of microvascular rat brain endothelial cells were exposed to either GSM1800 or UMTS-like signals at SAR levels of 0.4, 1.0, 3.0 and 8.0 W/kg. In addition, the study used a sham exposed control and a positive control introduced by heating the cell cultures to 40°C without EMF exposure. After 72 hours of exposure, RNA was extracted from the cells, hybridised onto a GeneChip® array, and up- or down regulation of genes was quantified using statistical software. Dr. Franke concluded that his results showed a number of genes that were up- or down regulated in the exposed samples, but indicated that these results were preliminary and awaited verification by quantitative RT-PCR.

Questions

Q: Using these results to predict any effect of RF fields on the blood brain barrier in humans would be difficult. It would seem that not enough information known [about the relation between the gene expression results and physiology of the barrier] to allow such prediction.

A: This comment is absolutely right. Transferring these results to issues of human well being is very difficult. It is not the point of the study. The goal of the present study is to study possible mechanisms by which RF fields can influence genes. If you can show that then you can go on to study possible effects on protein expression in this model or in an animal and then, ultimately, biological effects of RF energy in humans.

Q: Why did you not show dose-response data? My impression is that you have a minimum effect at an SAR of 3 W/kg and that the effect increases at 1 and again at 8 W/kg. This probably indicates a systematic effect. Then perhaps your whole conclusions can be affected. How can you explain this?

A: I would not put too much weight on this finding.

1-2

Effects of head only exposure to GSM-1800 or UMTS on the Blood-Brain-Barrier in vivo.

I. Lagroye, **University of Bordeaux 1, UMR5218 - IMS laboratory, bioelectromagnetics group, ENSCPB 16 avenue Pey- Berland, Pessac 33607, France and Ecole Pratique des Hautes Etudes, Bioelectromagnetics laboratory, 16 avenue Pey- Berland, Pessac 33607, France**

This study evaluated the permeability of the blood-brain barrier (BBB) and the presence of

degenerating neurons in rat brain after exposure to mobile phone signals GSM-1800 and UMTS at SARs of 0.026, 0.26, 2.6 and 13 W/kg. These studies were conducted over three years using a total of 1200 rats, and were controlled for age, gender, restrainer habituation, and exposure conditions; staining procedures and data analysis were done blinded. Dark neurons were identified using a) Cresyl violet and b) a second dye specific for degenerating neurons, Fluoro Jade B. Brain damage was evaluated immediately and 50 days after a 4-week repeated GSM-1800 and UMTS exposure (2 hours/day, 5 days/week) or immediately, one hour, and 1, 7 or 50 days after a single 2-hour GSM-1800 and UMTS exposure. Evidence for brain damage was mostly found 50 days after repeated exposures. Increases in the number of degenerating neurons and increased permeability of the BBB were sparsely found at various SAR levels and times after exposure, and in different brain regions depending on the parameters under study. Dr. Lagroye concluded that her results suggested no deleterious effects after a single exposure to GSM-1800 and UMTS signals, but up to a two fold increase in the BBB permeability was observed after repeated exposure to GSM-1800 and UMTS signals. This alteration of the BBB was not correlated with the presence of degenerating neurons, and the pattern of changes in the BBB with whole brain average SARs was equivocal.

Questions

Q: Your tables only showed whether a “statistically significant” effect is present, did not indicate the size of the effect. It would be important to show the effect size and dose-response functions. I suggest that if you find a scattering of positive associations with no dose response function and each association at the edge of statistical significance, then you probably have not found an effect. Are you sure that these are not a result of multiple comparisons and of no biological significance?

A: We found that the maximum increase was 2-3 fold. There was no dose response function, no trend of SAR dependency. The more convincing effect was found at the highest SAR level for which we have a hypothesis.

Q: I think that you need to look at the dose-response curve, to look at the dependence of the size of the effect as a function of exposure.

A: Yes, but the size of the effect is variable. We are trying to do more analysis, and find out what could be important for the interpretation. Independent confirmation would be needed before making a big story out of this.

Q: Have you any idea what is the local variation in SAR in the head? You only report mean SAR values.

A: This is the subject for future analysis. We are beginning to develop this kind of information.

Q. You suggested that the effect might be due to microwave hearing. Do you have any independent evidence that rats are hearing the pulses?

A: Very quick calculations suggested that the exposure to GSM signals at 13 W/kg might be in the range at which the microwave hearing effect could occur.

1-3

Effects of chronic whole body exposure to GSM or UMTS on the Blood Brain Barrier in vivo.

M. Stohrer, Institute of Animal Physiology, LMU Munich, Veterinärstrasse 13, 80539 Munich

This study examined the effects of chronic exposure to electromagnetic radiation of mobile phones (GSM, UMTS and Sham) on the permeability of the blood-brain barrier and the number of hippocampal CA1-neurons in the rat brain. Rats from three generations were continuously (24h/d) exposed under far field conditions at a whole body SAR of 0.4 W/kg. The integrity of the BBB was measured after four months of exposure within the generation F0b and F2, and after eleven months of exposure within Generation F0a. BBB integrity was measured by determination of the rate of influx of 14C-saccharose within seven defined brain areas of the left and right hemispheres. No differences were found between the influx rates in the three experimental groups (GSM, UMTS and Sham) in the rat generations that were investigated (F0 and F2). Neither increasing the exposure from four to eleven months, nor continuous exposure of different generations of rats resulted in significant differences of the influx of the tracer. Dr. Stohrer concluded that the lifetime exposure of rats to RF energy at a SAR of 0.4 W/kg caused no change in BBB integrity or in the number of hippocampal CA1 neurons.

Questions

Q: You have only one dose level, and cannot do a dose response investigation. Why did you choose such a low exposure level?

A: This is the maximum allowed for occupational whole body exposure. Space was limited and we could only do one exposure.

Q: Scientists have been arguing for more than 30 years whether microwave energy causes changes in the blood brain barrier. The controversy began in the 1970s when a rather poor study reported large effects of microwaves on the blood brain barrier. Later and better studies found either no effect or very small effects. And then the controversy started again with the studies of Salford, and we are still discussing the matter.

As a biologist do you think that this endpoint is significant enough to devote a lot of resources to? Other exposures that are known to disrupt the barrier are major stressors – high doses of toxic agents, high fevers, injections with hypotonic saline. You would have to nearly kill an animal to disrupt its blood brain barrier. Is it biologically justified to spend large resources in looking for small changes in the blood brain barrier which may or may not be produced by low levels of RF exposure as opposed to other, potentially more sensitive endpoints?

A: As I see it, all other effects of microwaves are also temperature dependent. With high doses [of RF energy] you see other effects in gene expression, calcium efflux, etc. If you have heating you have clear effects. If there is no heating everything is doubtful.

PANEL DISCUSSION to Session 1

Q: Do you find a difference in results with UMTS vs. GSM?

A: (several speakers). (Lagroye) We did not see consistent effects at SAR below 13 W/kg. We

see small differences in effects of the two signals at 13 W/kg but have to explore it further. (Franke) There might be some difference between UMTS and GSM but I have to get along with the PCR evaluation, this is just a hypothesis so far. The effects we see are really slight and maybe this is the reason we see small differences in effects between signals. (Stohrer) Our technical experts tell us that there is a difference in absorption of UMTS and GSM in rats due to the frequency difference, but we see no difference in effects.

Q: In the gene expression studies, what was the variation in results from experiment to experiment? Are the results reproducible?
A: (Franke) Unfortuately the gene chips are very expensive and I did not test for reproducibility of the results.
Q: Does anybody see any evidence from this session that would indicate the presence of a hazard to humans at exposure levels below ICNIRP limits?
A: (Lagroye) I think that we have already addressed this. In terms of statistical significance, small effects and nothing that could point to a real dangerous effects in the rat brain at exposures less than 13 W/kg. The answer is clear at least for us. (Franke) I do not think that it is possible to transfer my results to [predict] human health risks. (Stohrer) Effects are dose dependent, and at our dose we looked at different parameters and found no significant effects of the radiation on any of these parameters.

A: (Begley): as a biologist I would be surprised, if there were no effect at all. Tissues react to stimuli. The question is, where to draw the line between an observed biological reaction and pathological effects.

Q: Some time ago I heard a presentation on electro-gene therapy in which high frequency energy was used to increase the uptake of drugs. So it seems that high frequency radiation does have some effect on blood brain barrier. Can you comment?
A: (Begley) Certainly this is a use of electromagnetic radiation. Some of the best studies I know have been done at the University of Chicago where RF energy was used to open the barrier to try to allow drugs into the brain to kill a tumor. But the energies involved are enormous, far greater than involved in a mobile phone handset or living near a mast. You have to use very high energies to open the barrier. At the energies we are looking at here, there is very little in terms of opening the barrier. The heating effect is too low and the energy input into the tissue is too low to open the barrier.

Q: This morning we have seen a number of studies that have reported effects. Is there a mechanism within BfS to follow up these results? For example, the gene expression study seemed to indicate the existence of effects, but the results are the results of a single measurement, and they have not been repeated even once in the same lab. We cannot be sure that there is a real effect. It would be important to follow up these findings so that future standards setting organizations would not have to spin their wheels in trying to interpret the results. It is important at least to confirm the finding to make sure that we are looking at real effects as opposed to the effects of variability in a biological preparation. A single measurement in a one-shot experiment is not enough.

Comment (Lagroye) I think that the experiments that we did are not useless. The threshold for changing the blood brain barrier by thermal effects has been known for some time. Such high exposures [to RF energy] are not the case in real life. It was worthwhile to do more studies with

repeated exposures at low levels. I think that it is important that repeated exposures at low levels did not induce changes in the barrier. In the list of papers on the blood brain barrier was the study by Salford which found effects at low exposure levels. We did not find such effects and I think that the Salford study should not be discussed any more.

Session 2: Long term effects in animal models

Chair: G. Ziegelberger (Federal Office for Radiation Protection)

2-1

Effects of chronic whole body exposure to GSM or UMTS on learning and memory in vivo (Project 3)

M. Bornhausen, Institute of Animal Physiology, LM-University of Munich, Germany

In this project, three consecutive generations (F0, F1, F2) of WISTAR rats were continuously exposed to either GSM- or UMTS signals at an SAR of 0.4 W/kg and assessed for cognitive deficits using computer-controlled methods in test cages (Skinner boxes). The study design was double-blind, with sham exposed animals as controls. During 15-hour test sessions, the number of lever presses, food reinforcements, and test efficiency of each animal were recorded, together with the distribution of time intervals between consecutive lever presses during test sessions. The study, covering three consecutive generations of rats, found no significant differences in operant-behavior performance or memory in GSM- or UMTS-exposed rats in comparison to sham-exposed animals.

Questions

Q: Would you like to comment on the studies by Lai in Washington, which reported effects in exposed and sham exposed animals using water maze, and the studies Cobb in Texas that used a radial maze system that did not find effects.

A: There are clear cut arguments in favor of operant behavior studies rather than using qualitative testing procedures including water maze studies which are very much dependent on investigator bias. Operant behavior studies nowadays are easy to do with modern technology. I personally would be very hesitant to suggest further experiments concerning electromagnetic fields [on behavior]. I would prefer to shift back to toxicology studies.

Q: What other kinds of toxic exposures would produce effects that you could detect with your studies?

A: My former studies involved animals exposed to methyl mercury. We exposed rats to 40 micrograms per kilogram body weight of methyl mercury and were astonished to see very clear effects.

2-2
Effects of chronic whole body exposure to GSM or UMTS on immune response and stress (Project 3)
C. Wöhr, Institute of Animal Physiology, LM-University of Munich, Germany

This study examined the chronic effects of mobile telecommunications signals on the immune system and stress parameters in Wistar rats. The 294 female rats were exposed either to UMTS (900 MHz) or to GSM (1900 MHz) signals at an SAR of 0.4 W/kg, with a sham-exposed control group. All animals were born in the respective field and remained there until the beginning of the experiment. Animals were examined from two generations (F0, F2) after exposure periods and in different age groups. The rats were immunised with the antigens Ovalbumin (OvA) and chicken immunoglobulin Y (IgY) in combination with the lipopeptide adjuvant Pam3CysSerLys4, and blood samples tested for total IgG and specific antibody titers. In double-blinded studies, ACTH was applied intraperitoneally as a standardised stressor. Serum corticosterone was measured in blood samples by an indirect competitive ELISA-system. Dr. Wöhr reported that significant differences could only be found in some cases in the F0b generation, but they could not be reproduced in generation F2 for the same exposure duration. In these studies, chronic exposures of rats to GSM and UMTS signals did not alter the antigen-specific immune response or stress parameters in the animals.

Questions
Q. Were the chambers indistinguishable – did you know which chambers were real exposure or sham?
A: The exposures were in a separate room from the investigators and we did not know which animals were sham exposed and which were exposed to RF radiation.

2-3
Influence of HF-EMF of mobile communication systems on the induction and course of phantom auditory experience (tinnitus) (Project 4)
M. Knipper/L. Rüttiger, Hearing Research Center, University of Tübingen

The potential effect of high frequency electromagnetic waves on the induction of spontaneous tinnitus was studied in 160 rats that were exposed over 4 weeks (5 days per week), 2 hours per day, to GSM 900 MHz at 0.02, 0.2, 2 and 20 W/kg to the area of the head and neck. Animals were exposed in a cage system using an antenna fastened around the neck, targeting electromagnetic exposure to the head area. Additional animals were sham-exposed controls; experiments were done blinded. Temperature monitoring of anaesthetized animals revealed no significant thermal effects at SARs below 20 W/kg; at the highest exposure level there was a 2 degree increase in temperature beneath the antenna in the neck of the animals with no detectable increase in core temperature. The cochlea, inferior colliculus and auditory cortex were removed from 80 rats and the expression of activity-dependent genes (BDNF, cFos und Arg3.1) was studied using semi-quantitative RT-PCR to examine for possible changes in gene expression that occurs with onset of tinnitus and the associated neuroplastic modifications. An additional 80 rats were trained in a behavioural protocol to test for perception of tinnitus. The tinnitus behaviour was then tested before each exposure, directly after exposure, as well as after a recovery phase. The experiments were performed in a blinded manner. Initial statistical analysis (t-test) did not reveal statistically significant effects on gene expression or on tinnitus

sensation in the animals

Questions

Q: Is that 20 W/kg whole body average to the animals?
A: No, this is under the antenna.

Q: I noticed that the jackets with the antennas covered part of the ears. Did they affect hearing?
A: No, we checked that. The jackets did not cover the ear canal.

Q: The high local SAR might have led to cutaneous sensation of heat, perhaps even discomfort. Could that be a confounder of your results?

A: We did not find any effect, even though this system is very sensitive.

Q: Maybe I misunderstood your results – you did find one radiation dependent effect?
A: No, not in these studies.

2-4
Influence of high frequency electromagnetic fields on spontaneous leukaemia (Projects 5,6) and on the metabolic system (Project 7)
A. Lerchl (Jacobs University Bremen)

Project 5b (AKR mice and GSM electromagnetic fields)
Several reports indicated that non-thermal electromagnetic radiation such as from mobile phones and base stations may promote cancer. Therefore, it was investigated experimentally, whether 900 MHz electromagnetic field exposure influences lymphoma development in a mouse strain that is genetically predisposed to this disease. The AKR/J mice genome carries the AK-virus, which leads within one year to spontaneous development of thymic lymphoblastic lymphoma. 320 unrestrained female mice were sham-exposed or exposed (each n = 160 animals) to GSM like 900 MHz electromagnetic fields for 24 hours per day, 7 days per week, at an average whole body specific absorption rate (SAR) value of 0.4 W/kg. Animals were visually checked daily and were weighed and palpated weekly. Starting with an age of 6 months, blood samples were taken monthly from the tail. Animals with signs of disease or with an age of about 46 weeks were sacrificed and a gross necropsy was performed. Electromagnetic field exposure had a significant effect on body weight gain, with higher values in exposed than in sham-exposed animals. However, survival rate and lymphoma incidence did not differ between exposed and sham-exposed mice. These data do not support the hypothesis that exposure to 900 MHz electromagnetic fields is a significant risk factor for developing lymphoma in a genetically predisposed species, even at a relatively high exposure level.

Project 6 (AKR mice and UMTS electromagnetic fields)
The present study investigated whether chronic exposure to EMFs of the UMTS (Universal Mobile Telecommunication System) influences the development of lymphoma in the AKR/J mouse. Unrestrained mice were chronically sham-exposed (n = 160) or exposed (n =160) in identical exposure systems (radial waveguides) to a generic UMTS test signal (24 h per day, 7 days per week, 0.4 W/kg SAR). Additionally, 30 animals were kept as cage controls. Animals

were checked visually each day and were weighed and palpated weekly to detect swollen lymph nodes. Starting at the age of 6 months, blood samples were taken from the tail every 2 weeks to perform differential leukocyte counts and to measure the hematocrit. Visibly diseased animals or those older than 43 weeks were killed humanely, and tissue slices were examined for metastatic infiltrations and lymphoma type. The study was performed in a blinded way. Cage control animals had a significantly lower growth rate than those kept in the radial waveguides. The number of ill animals, the mean survival time, and the severity code of the disease did not differ between the experimental groups. Therefore, the data show no negative effects from exposure and corroborate earlier findings in AKR/J mice exposed to GSM EMF.

Project 7 (Metabolism)

At present, most experimental research projects could not identify increased risks for malignant diseases due to exposure to radiofrequency electromagnetic fields (RF-EMF). However, some results have indicated that non-thermal RF-EMF affect the body weight of hamsters and mice at 383 and 900 MHz, respectively (Lerchl et al., in preparation; Sommer et al., BMC Cancer 4:77, 2004). At 1800 MHz and at UMTS frequencies, no such effects were seen. It was argued that these effects may be caused by the energy absorption of RF-EMF which leads to changes of the metabolism of the animals. According to the hypothesis, absorbed RF-EMF energy causes a shift of energy utilization of food, i.e. less energy is used for heat production, and thus more energy can be converted to fat or muscle tissue. To test this hypothesis, Djungarian hamsters were exposed to 900 MHz RF-EMF (0.08, 0.4, and 4 W/kg) while the production of carbon dioxide and the consumption of oxygen were registered continuously. Food and water consumption and energy utilization were measured under exposure and sham-exposure conditions in blinded experiments. The experiments were performed in a staggered design, i.e. one week of sham-exposure and one week of exposure alternate. Infrared images were taken of all animals to check whether exposure has an effect on skin temperature and the animals were weighed weekly. The results obtained so far demonstrate that the exposure system is working properly, and that the variations of the parameters are small enough to detect changes in the order of 15%. The experiment is currently running and will end in early 2008.

Questions

A long discussion ensued about effects of RF energy on energy balance in animals and the possible relation to the effects seen (increases in lifespan, weight gain in the exposed animals).

Q: About 30 years ago I did a study on shift workers, which found that they had a higher body weight than nonshift workers even though their caloric intake was the same. Have you looked at the effect of changes in diurnal rhythm in changes in body weight in the exposed animals?

A: No, that would be very hard to do.

2-5

Influence of chronic exposure to high frequency electromagnetic fields on fertility and development in vivo (Project 8)

A. Lerchl, Jacobs University Bremen gGmbH, 28759 Bremen, Germany

This project searched for possible effects of long-term exposure of mice to UMTS signals on fertility and development. Adult male (one per cage) and female mice (two per cage) were

exposed 24 hrs per day, 7 days per week at SAR levels of 0 (sham), 0.08, 0.4, and 1.3 W kg^{-1} in a blind fashion. For each SAR value, 32 cages (96 animals) were used. The body weight was checked daily. Shortly before the end of the pregnancy, one female per cage was sacrificed, and the number of fetuses was counted, while macroscopically visible malformations were evaluated. The weights of all fetuses and of the uteri were also recorded. The remaining female and the male were kept in the cages. After delivery, the number of pups was counted and their development was observed (body weight, time point of eye opening, reflex tests). After weaning, the parental animals were sacrificed and examined for pathological abnormalities. The males' testes were analyzed for the number of sperm in the tubules. From the pups of each generation, males and females were selected randomly for the next generation. Unfortunately, the numbers of surviving pups of the first litters were always too low to recruit enough animals for the next generation, despite the high numbers of pups per litter, as counted immediately after birth. Therefore, a second pregnancy had to be included in the experimental design which yielded sufficient numbers of surviving pups. The experiment is now completed. The final results and the statistical analysis will be calculated before the code will be broken.

Questions

Q: Did you do any investigation on the fetuses?
A: We have not yet analyzed the fetuses.
Q: Was there any difference in the sex ratio of the fetuses?
A: There was no difference.
Q: There have been reports of malformed sperm in men using mobile phones. Did your results show any differences?
A: We saw no effect.

Panel Discussion to session 2

A discussion was held about biological variation as a potential factor in contributing to some of the positive findings in the studies reported in the session. Referring to the gene expression studies, a member of the audience called for an examination of the variation in expression of genes from one experiment to another in unexposed animals, which "is a different matter than normal biological variability".

Q: All long term studies involving carcinogenesis have been negative apart from the PIM-1 mice in the experiment done by Repacholi's group. With respect to low-frequency studies, nearly all animal studies for initiation and promotion have been negative. But IARC has decided that ELF magnetic fields are "possible" (2B) carcinogens. Should we continue to do long-term animal studies? What good are we going to take from these animal studies?

A: The community of epidemiologists does not completely agree that the association between ELF-field exposure and leukemia is valid. With the epidemiology studies we are only talking about a few excess cases a year associated with ELF field exposure. Doing animal studies to detect such small increases in risk will be very difficult because of the number of animals.

Q: We have heard a lot today about GSM and UMTS -- will we have to repeat all of these studies when every new technology appears?

A: I think that for political reasons it will be necessary to repeat these studies with new technologies. Another speaker expressed the view that each different frequency is a different

entity that must be examined separately.

Q: Do we have any rationale to say that animals are more or less electrosensitive than humans? We have no effect in the animals – can we say that we do not expect effects in humans?

Comment: From a radiation protection point of view, it would be problematic to conclude that every frequency must be considered separately. We have to consider mechanisms. We have been asking all day whether there might be some mechanism that would lead to differences between UMTS and GSM radiation, but I have not seen any evidence today [for any such mechanism that would lead to] a difference. If we cannot find evidence that this major difference in signal quality affects the outcome, this does not challenge the hypothesis that the main interaction mechanism is thermal.

Q: Is the question of fertility and development closed?

A: (Bornhausen) Behavior has been particularly sensitive. However we should switch from observational studies on behavior to computer-assisted quantifiable measurements. We should focus on behavioral studies that have proven their sensitivity in earlier studies not involving RF energy.

Session 3: Epidemiology - Adults
Chair: Dr. Michaela Kreuzer, Federal Office for Radiation Protection

3-1

Feasibility of a cohort study of persons exposed to high frequency electromagnetic fields in an occupational setting in Germany

Jürgen Breckenkamp[1], Gabriele Berg[1], Eva Münster[2], Joachim Schüz[2], Brigitte Schlehofer[3], Maria Blettner[2]
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3 Unit of Environmental Epidemiology, German Cancer Research Center, Heidelberg, Germany

The aim of this study was to evaluate the feasibility of a cohort study on health risks due to radio frequency/microwave exposure. Ideally the exposure should be similar in frequency and quantity to the exposure to mobile phones, because these conditions would allow a transfer of results to the exposure to mobile phones. Twenty-three occupational settings with potentially exposed workers were considered. The vast majority of occupational groups had to be excluded due to small numbers of exposed subjects or exposure levels only marginally higher than for the general public. Three groups were selected for further evaluation based on expert ratings, literature reviews, and according to a developed criteria catalogue. The cohort of workers on dielectric heat sealers showed the greatest limitations (very small number of cases, small companies widespread all over the country, cooperation with companies was judged as problematic, the exposure from the heat sealers was not comparable to exposure to users of mobile phones, mixed exposures to other potentially hazardous substances, e.g. plastic vapors) although exposure of the workers to RF energy was highest in this group. The strength of the cohort of amateur radio operators was the large number of persons with a uniform access. Disadvantages were the irregular exposure with most often low levels and the lack of comparability with the exposure to mobile phones for the vast majority (>95 %) of this cohort. The advantage of the cohort of personnel of transmitting plants was the quality of retrospective exposure assessment. Weaknesses were the low levels of exposure, the very small numbers of exposed and the fact that exposure is not comparable with exposure to mobile phones. No group of subjects could be identified to determine without major problems any increase in morbidity or mortality risk associated with RF-EMF exposure. No cohort was found with an exposure to radio frequency electromagnetic fields similar in frequency range and exposure level to mobile phones. The present authors recommend a cohort study of users of mobile phones as a fourth alternative.

Cohort Study on Mobile Phone Users (COSMOS)

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The aim of the study was to evaluate whether it was feasible to participate in an international prospective cohort study of cellular telephone users (Cosmos) under the constraints of the German legislation on data confidentiality, disease data availability, cellular telephone data accessibility, and compliance in the German population to establish a large cohort of 50,000 subjects. In a pilot study, 5,000 potential cohort members stratified by age and gender were invited applying three alternatives of enrollment; 1,000 subscribers were selected from each of the four German network operators (additionally stratified by the amount of monthly cellular telephone use), with two different letters,, another 1,000 drawn randomly from a population register. Overall response rates were low (5-14%). While response rates were better using the population sample, the samples from the network operators included more regular cellular telephone users. The feasibility study showed that it was possible to establish procedures for data exchange with all four network operators,. Follow-up is not feasible for many of the diseases as no population based disease registries exist, except for a few exceptions. Furthermore, the study design and its related contact procedures were approved by all relevant data protection authorities. Hence, in principle, all requirements for a successful German participation in the international framework were fulfilled. However, the low response rate of subjects in the feasibility study indicated that a very high budget would be required to create the cohort for the full study.

Questions

Q: Why do you conclude that you would have selection bias [in a prospective cohort study]?
A: We were not sure whether we could recruit a random sample of mobile phone users in each exposure group (low, medium, high) from population registries because we would have to inform the subjects that our study is looking for effects or mobile phone use.
Q: Is the low participation rate [that you found] typical of similar studies in Germany?
A: Yes, for case-control studies in Germany I expect that about 20% of individuals contacted once will participate. With a lot of additional effort we can eventually get 50-70% response rate, but this is not feasible in cohort studies. In principle it would be possible to include physicians in the cohort and to obtain health records of individuals from their physicians – but that would not be economically feasible in a cohort study of 50,000 subjects. It would require an immense effort.

A: Additionally, in this case it was not a single questionnaire, but people were asked to participate in a long term study. That changed completely the response rate.

3-2

Case-control study on brain tumors and mobile phone use (INTERPHONE) (Project 11)

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This study is part of a multinational case-control study on cellular telephones and other exposure sources of radio frequency electromagnetic fields (RF-EMF) and the risk of brain tumors including acoustic neuromas (AN). In this population-based study in three German regions, all incident cases of the respective tumors in 30-69 year old patients were ascertained during 2000-2003. Controls matched on age, gender, and region, were randomly drawn from population registries. In total, 366 glioma cases, 381 meningioma cases, 1,494 brain tumor controls, 97 AN cases, and 194 AN controls were interviewed. Overall use of a cellular phone was not associated with brain tumor risk, the respective odds ratios (OR) were 0.98 (95% confidence interval: 0.74-1.29) for glioma, 0.84 (0.62-1.13) for meningioma and 0.67 (0.38-1.19) for AN. Among cellular phone users of 10+ years, a non statistically significant association with an increased risk of 2.20 (0.95-5.11) was observed for glioma. No increased risk was observed for meningioma or AN. Neither use of a cordless phone nor having a cordless phone base station close to the bed was related to any increased tumor risk. High occupational RF-EMF exposure mainly from the use of communication devices yielded nonstatistically significantly increased ORs of 1.22 (0.69-2.15) for glioma, 1.34 (0.61-2.96) for meningioma and 1.45 (0.51-4.19) for AN. These results are broadly in line with other studies in that they do not suggest an increased risk with overall cellular telephone use. For heavy long-term use of cellular and cordless phones and long-term high occupational exposures the study leaves open the possibility of a risk increase and further study results need to be awaited before drawing firm conclusions.

Questions

Q: I do not understand the statement in your abstract that you found an association with an OR of 1.22 with confidence intervals from 0.69 to 2.15. This is not statistically significant. What do you mean by an association?
A: The association is not statistically significant. The OR is a measurement for an association, whether negative, null or positive.

Q: Do you know of any environmental effect that has been associated with a solid tumor in such a short period of time? Your average [exposure] period is a few years.

A: All I said was that we found no statistically significant increase in risk so far.. From the current study we can not say anything about very long time exposure.

Comment: The original hypothesis was that [use of mobile phones] had a promoting effect, not an initiation effect. In that case we should have been able to see some effect in the epidemiology data.

3-3
Case-control study on uveal melanoma and radio frequency radiation (Project 12)
A. Stang, IMEBI, University of Halle-Wittenberg

In this case-control study, 455 uveal melanoma cases and 827 population-, 180 ophthalmologist-, and 188 sib controls were interviewed, using the questionnaire instrument of the INTERPHONE study for exposure assessment related to mobile phone use. Odds ratios and 95% confidence intervals were calculated with conditional logistic regression accounting for the matching factors. The response proportions were 95% for the cases, 57% for the population and sibling controls, and 52% for the ophthalmologists' controls. Overall, 43% (284 out of 663) of all population controls who refused to participate filled in a short questionnaire. The age- and sex-standardized prevalence of regular mobile phone use was considerably lower among nonparticipating controls who completed this short questionnaire than participating population controls (27%, 95% CI 18-36% versus 36%, 95%CI 32-40% respectively). The study found no consistent pattern of an association between mobile phone use and risk of uveal melanoma, although the precision of the estimates in some cases was reduced by small numbers of subjects in groups. A few increased odds ratios were found with use of cordless phones, but these were based on groups with few subjects and subject to large uncertainties.

Comments
I would like to thank you for putting so much effort into explaining how you did the study. It is important to see how much work and how difficult it is to take this data, and at the end of the day we have very small numbers and it is difficult to know what to say.
(Response): I am a bit afraid to go into too much detail about the analysis. After all of the effort we put in, we still do not get enough people to participate.

Questions
Q: Your first study (Epidemiology 2001; 12; 7-12) found associations between uveal melanoma and mobile phone use. How did you measure exposure in that study?

A: The first study used a rough 1-2 page section in a questionnaire that focused on exposure in the workplace only. Due to the exposure assessment, detailed analyses on mobile phone use were not possible. In addition, the study size was too small.

Panel discussion to Session 3

Comment: There are problems with case-control studies in the literature such as selection and recall bias. These problems will be overcome in a cohort study, and for that reason it is important to do cohort studies. So I would recommend enlarging the [international] cohort study that is about to start.

Q: These proposed cohort studies will be very expensive. My question as a taxpayer is why [do them]? Unless there is a reason to believe that there may be a problem why embark on such a

long study?

A (Schlehofer): For a scientist it is difficult to say that we should not do more further research. But I do not think that we can do better with a cohort study in Germany than we have so far with case control studies. I do not think that we should do a cohort study right now.

Q: We have invested a lot of resources in mobile phone epidemiology studies. I wonder why epidemiologists here do not defend these studies? What is the justification to continue with this line of approach? Also, how will we know whether the endpoints we choose now are of interest in 25 years?

A (Schlehofer): We have learned a lot from the studies. We have learned that no risk from mobile phones can be seen up to now, and we send out the message out to the community that people should not be worried about brain tumors.

Comment: We have contributed reassurement that there is no major risk such as cancer from smoking.

Comment: If the forthcoming summary analysis of the Interphone study discloses a statistically significant increase in risk for long-term use, which might be anticipated from the hints in some of the previously published parts of the Interphone studies, then politically it will be impossible not to continue epidemiological studies of some sort.

Session 4: Children – Age Dependent Effects
Chair: B. Pophof, Federal Office for Radiation Protection

4-1
Case-control study on childhood leukaemia and proximity to radio and television transmitters (Project 13)
H. Merzenich[1]/S. Schmiedel[1,2]
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A case control study was set up in Germany to determine whether there is an increased risk of childhood leukaemia in populations exposed to RFR from TV and/or Radio towers. A total of 25 regions with high power broadcasting stations have been selected in West-Germany. and who lived in the vicinity of these towers. A total of 1.994 eligible cases have been identified from the German Childhood Cancer Registry, who are children aged 0 to 14 years with a primary leukaemia diagnosed between 1984 and 2003. Three controls per case have been individually matched by age at diagnosis, sex, time of diagnosis and study area. The study focuses on an individual retrospective exposure assessment using data from transmitter network operators, with calculated values for the exposure level for the place of residence at the time of diagnosis. The study started in March 2005 and is anticipated to be completed in December 2007.

Comments

You cannot pool low-gain with high-gain antennas in exposure assessment, since the transmission patterns are very different.

Questions

Q: You compared measured with calculated fields and have not-so-convincing correlations. Have you correlated measurements outside houses with those inside the houses? That will lead to significant exposure misclassification.

A: As we will use a classified analysis with the 90% quantile as threshold for being exposed the correlation (in all analysis > 0.8) is not the best measure to judge misclassification. In a classified analysis the sensitivity and specificity are more appropriate. The sensitivity shown is between 45-65% and the specificity is in all subanalysis >90%. A high specificity is essential as only 10% of the participants are exposed and high specificity will not have much impact on the power of the study even when sensitivity is low. This we have shown in the table of power of the study when taking misclassification into account. The improvement of this study is the usage of calculated field strength outside of the place of residence instead of distance alone. It is true that we can not assess the misclassification due to shielding of a house, because we have no measurements. But we still think the exposure assessment used in this study is a major improvement compared to previously applied metrics in RF-EMF epidemiology.

4-2
Investigation of age-dependent effects of HF-EMF based on relevant biophysical and biological parameters – a realistic model of children´s head and source of RF-radiation (Project 14)
A. Christ, Foundation for Research on Information Technologies in Society and University of Zürich, Zürich

This study quantified the SAR and RF induced temperature distribution in anatomically correct head models of children in comparison to adults. The study used recent dielectric data from animal studies, and took into account age and temperature dependence of the dielectric tissue parameters. The peak spatial averaged SAR, the exposure and the temperature increase in target structures (pineal gland, the hippocampus, the hypothalamus, the skull and the bone marrow) were calculated using the FDTD simulation platform SEMCAD X. The simulations were validated through temperature measurements in the auditory canal and on the skin surface of adults and children as well by SAR measurements in a phantom model of a child'smml head. Validation of the peak spatial average SAR in the heads of children was done using an experimental phantom based on MR images of a three year old child. The thermal simulations were validated by measurements of the temperature in the auditory canal and on the skin surface of adults and children during exposure with a conventional mobile phone and a generic phone model fed with an external RF generator. The simulation results show a small effect of age on the peak spatial average SAR. The exposure of specific regions of the brain depends strongly on their position in the head and their distance to the RF source. Consequently anatomical differences of adults and children can play a significant role with respect to the local exposure, which should be considered for epidemiological studies. A relevant temperature increase due to RF exposure could not be observed in the simulations and in validation measurements.

Questions

Q: Have you considered the effects of blood flow in the phantoms?
A: We are taking that into account in the numerical simulations. The phantoms are used to validate SAR calculations and do not include blood flow.

Q: I wonder why you apply a US standard which is not relevant for Europe. In Europe we have ICNIRP, which takes a different approach than the IEEE and US standards. You can get considerably different results if you average over 10 grams of contiguous tissue rather than over tissue cubes. In averaging over a cube, you are ignoring anatomical features. Proper averaging procedures [following ICNIRP] should be easy to implement by your group.
A: There is no software available which is suitable for averaging over contiguous regions of tissue. This has been under discussion for a long time in our group.

Comment: I am not sure of the relevance of this to health hazards. WHO and other agencies have concluded that the hazards of RF energy are by and large related to excess heating. Small variations in SAR, if the heating is negligible as it is with mobile phones, would not appear to have any health relevance as long as we are talking about thermal hazards, and there is no basis to speculate about nonthermal hazards.

FINAL DISCUSSION W. Weiss

Introduction (Weiss) This program is not a basic research program. It is driven by concern of people. Our political leaders want a clear answer whether or not we are presently protecting the public adequately. We need to answer the over-riding question: are the limit values of exposure guidelines safe or not?

I heard concerns in the first session whether the blood brain barrier is a suitable endpoint. Do we stop here with this line of research? Then we heard about animal experiments in which genetically modified animals were exposed for several generations to RF fields. My impression is that we tried very hard [but failed to find effects] – should we continue with this? We also heard that we tried to put together a cohort for a prospective cohort epidemiology study and we failed. Is this the end of science in this area? The results presented in this workshop which do not show an effect, are important for this program. Experiments that repeated previous work with a clear result are important because they decreased uncertainties.

Two participants asked, how we would justify expenditure in the future to look for long term effects as we do not have evidence that there are any. But this is a scientific kind of question. If policy makers do not get a clear answer from us they will continue on their own to answer the questions which society has. The only way to channel that is to tell them the best way to tackle the problem. Shall we continue with animal experiments, continue with epidemiological studies or do we improve our cancer registry? What is the best way to go ahead? Where do we still have gaps?

Comment: Two suggestions. (1) It is important to maintain efforts in risk communication, (2) it is important to maintain competence in BfS on this issue.

Comment: There is a segment of the population that is convinced that there are harmful effects of RF energy. We can communicate to the public about the current state of the knowledge but say that it is too soon definitely to confirm or rule out possible carcinogenic effects from long-term exposures.

Comment: Science cannot answer all questions in total there will always be gaps. My personal point of view is that Interphone was important to do, but given the latency of cancer perhaps it was started too early. Moreover the usage of mobile phones will change with time.

Comment: When we began the Interphone study there were epidemiology studies (Hardell) reporting large risks after short term use of mobile phones. The Interphone studies convincingly show that there is not detectable risk increase after short term exposure. For the period that we have been able to study there is no evidence, apart from Hardell's work, for short term increases in cancer risk, but they leave the question open about long term effects. Research done both on animals and cells and epidemiology studies tells us that we do not have to worry. But there are gaps. We have no information about real long term effects, and no data about exposures to children.

Comment: Perhaps the best thing that we could do would be to strengthen tumor registry.

Comment: negative results are not a failure in science – only difficult to publish sometimes.

Changes in gene expression should be followed up, otherwise we may miss a relevant process.

A: Without a clear impact on something that is relevant to health it is fundamental research and does not focus on the question we have to answer. As a physicist I start out with the idea how something is functioning. I do not have the sense that the gene expression investigators are doing this. They are looking for many effects in a multitude matrix, but I cannot get them to tell me what their hypothesis is. There is no idea what the health relevance of the observed effects might be.

Comment: I got the impression, that experimentalists are looking at the epidemiologists for further input and vice versa. Science is at a point where it should think for a while before continuing research on this topic, and in the meanwhile there is the need for risk communication. Evidence for health relevant effects from all areas of research is rather weak. We are not searching for a big risk.

Comment: when research on EMF started, it was scattered and often unrelated to health. Nowadays ongoing research programs on a whole include very good science and are in most cases directly related to some health endpoints. This is a success. The fact that you have not identified a hazard, is not a failure of science, but maybe science is just not able to measure them – or maybe there is nothing to measure. It is necessary to share information in international context, e.g. at the WHO or the EMF-project.

Comments from several participants:
One persistent gap is the research on children, e.g. neurological effects.

Comment:
We need to have more information about overall EMF-exposure.

A: there are some dosimetric projects on multiple sources, but they do not cover the whole frequency range.

Comment:
Another important topic is reduction of exposure.

Comment:
It is necessary to interlink results from different areas to get a clearer picture.

<u>Conclusions from the comments for future work:</u>

1) It is time for consolidation
2) Do not just continue “because science is nice”
3) Persistent gaps: children, combined effects, long term effects
4) Optimization of exposure
5) Maintain efforts in risk communication.