Rapporteur's reports

International Workshop "Open Questions in the Research on Biological & Health Effects of Low-Intensity RF-EMF"

Stuttgart, November 17-19, 2008

CHILDREN & OTHER SPECIFIC GROUPS

Chair: Bernard Veyret,

Rapporteur: Kenneth R. Foster, Department of Bioengineering, University of Pennsylvania, Philadelphia PA, USA

This session dealt broadly with the possibility that children and other sensitive groups might be particularly at risk from RF energy absorption.

The first paper in the session was a dosimetric study entitled "RF-Absorption and Temperature Distribution in Heads of Children" and was presented by **Andreas Christ** (IT'IS Foundation, Zürich). Dr. Christ reviewed the extensive studies he and his colleagues at IT'IS performed to determine the SAR produced in the head by mobile handsets, and the corresponding temperature increases in their heads. He reviewed several factors that determined SAR in the head from mobile phones, including phone design and anatomical differences between adults and children. His work found no characteristic age-specific differences in the peak spatial average SAR in the head. However some regions of the brains of children receive a higher SAR than in adults because of their smaller heads and thinner skulls, which results in the antenna of the handset being located closer to the brain of children vs. adults. Christ reported experimental measurements and modeling calculations that showed that the temperature increases in the head from RF-exposure from use of a mobile phone are small, e.g. 0.05 C in the auditory canal or cheek; with temperature increases being no greater in children than in adults. He noted also that ICNIRP whole-body exposure limits are "not conservative" for children in the frequency range between 1.5 and 4 GHz, referring to the fact that whole-body exposures to children in this frequency range at the ICNIRP limits might result in total body SARs that are 50% higher than ICNIRP fundamental restrictions.

In the discussion following this presentation, the question arose: what level of detail is needed in dosimetric data from mobile phones? One participant suggested that the public wants to have detailed information about the SAR distribution in the brain from a mobile phone handset. Another participant took issue with this suggestion, and expressed the view that detailed SAR distributions, provided that the basic restrictions of ICNIRP are maintained, are impossible, even for experts, to interpret in terms of potential health significance and consequently such detailed information would be of little benefit to the public.

Martin Röösli (Institute of Social and Preventive Medicine, University of Bern), in the second paper of this session ("Studies Investigating Effects of Radio Frequency Electromagnetic Fields on Children") reviewed 19 epidemiological studies related to RF exposure to children. The studies generally showed no cognitive effects of RF energy exposure on children, apart from one study, which reported effects of use of a mobile phone on the EEG. A recent (2008) study by Divan et al reported that the use of a mobile phone by a pregnant woman during pregnancy was associated with later behavioral problems in the child, however Röösli noted some of the difficulties in interpreting the study. One major difficulty with the study, he noted, was its use of a questionnaire to assess a mother's use of mobile phones during pregnancy. Röösli also noted that some positive associations that had been reported previously between residence near RF broadcasting facilities and childhood leukemia could not be confirmed by two recent studies (Ha et al 2007 and Merzenich et al 2008).

A short discussion took place following this presentation about needs for future epidemiological studies in this field. Prof. Röösli suggested that two different kinds of studies need to be done: epidemiological studies with exposure to mobile phones during pregnancy, long term (prospective cohort) studies. He also expressed the view that additional behavioral studies need to be done as well.

Geza Benke (Monash University, Australia) presented his paper “Cognitive Function and Mobile Phone Use in Schoolchildren”, about his study (MoRPhEUS). The study measured a range of cognitive outcomes in children 11-15 years of age as related to use of mobile phone handsets as assessed by means of a questionnaire. The study found a number of statistically significant associations between use of mobile phones and some measures of cognitive performance: use of mobile phone was associated with “faster and less accurate responding on higher level cognitive tasks” which “may be due to more impulsive behavior with increasing use” or “learned through frequent use of a mobile phone”. Dr. Benke noted that the effects were similar regardless whether the handset was used for calls or for text messages, which he interpreted as indicating that the observed effects were not related to exposure to RF energy.

Heidi Danker-Hopfe (Charite Universitaetsmedizin Berlin) presented her paper entitled “Sleep and RF-EMF - Are Elderly Subjects at an Increased Risk for Sleep Disturbances?” She reviewed the literature related to cell phone use and sleep disturbances. She described the literature as being very mixed but failing to show consistent changes in sleep or EEG with use of mobile phones. She described her study on 376 subjects, representative of the German population, aged between 18 to 81 years. The study found that older subjects were more concerned about possible health effects resulting from mobile phone base stations and mobile phones than younger ones. Her study found a decreased sleep quality, as measured by a range of measures of sleep efficiency and sleep latency, in subjects who were worried about health risks from mobile phone base stations. However, she concluded, neither GSM 900 nor UMTS exposure has a short term effect on sleep (as opposed to effects of health concerns about mobile base stations), and her present results do not support the view, expressed by some members of the public, that RF-energy exposure produces disturbances in sleep.

Carmela Marino (Casaccia Research Center, ENEA, Rome) presented a paper “Measures for the Exposure of Newborn Animals to Wi-Fi Signals”. The study, which is still ongoing, involves exposure of mice to Wi-Fi signals (2462 MHz, 0 to 4 W/kg, 2 hr/day, and 5 days/wk). Her paper focused on experimental and numerical dosimetry and exposure methods being used in the study.

Rapport on the workshop session "Long-Term Animal Studies and RF"
Chairs: Alexander Lerchl and Jochen Buschmann
Rapporteur: Jochen Buschmann, Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany

The main questions to be addressed by the workshop session "Long-Term Animal Studies and RF" were:
1. Can animal studies of one or more generations be considered as "long-term" studies regarding the situation with humans?
2. Is thermal regulation a mechanism that has to be taken into account at exposures below the guidelines?
The workshop session included six presentations. In the following, only the main conclusions of the presentations are reported. For more detailed information, the interested reader is referred to the abstracts and the presentations, which are available at: http://www.fgf.de/english/research_projects/ws19.html.

The first presentation of this workshop entitled "Measures for the Exposure of Newborn Animals to WIFI Signals" was given by **Carmela Marino**. The presentation focused on the development of dosimetric methodologies and experimental procedures for whole-body RF exposure of newborn mice, and it could be shown that that it is possible to perform experiments with newborn animals under controlled EM field conditions, so that specific procedures can be adopted in the future.

In the next presentation, **Clemens Dasenbrock** and **Jochen Buschmann** gave an overview on "In vivo Studies with RF-Exposure at the Fraunhofer Institute in Hannover". The main focus of this presentation was on the results of the recently finalized EU project PERFORM-A, which investigated potential carcinogenic and co-carcinogenic effects in animal models. As an overall conclusion, three out of four studies produced no evidence of any effect of the exposure (GSM- and DCS- type) on the incidence or severity of any neoplastic or non-neoplastic lesions (with one equivocal finding in one study). The only effect observed was a borderline one in the study investigating effects on the DMBA-induced mammary

tumour response. Additional studies on micronucleus formation in mice did not demonstrate a genotoxic effect nor an influence on red blood cell formation after similar RF-exposures of 1, 6 and 104 weeks.
In addition to these investigations, a summary was presented of the results of other recent studies performed at Fraunhofer ITEM addressing subchronic effects incl. immunotoxicity, as well as fertility, pregnancy, developmental neurotoxicity, and genotoxicity, some of which are still ongoing.

Alexander Lerchl reported on "In vivo Studies with RF-Exposure in Bremen". A number of studies were performed there to address the possible effects of RF-EMF on mice. In one study, AKR mice, which have a high incidence of spontaneous lymphomas, were chronically (life-long) exposed to GSM-modulated signals. As in the earlier investigation, no harmful effects were observed.
In a multi-generation study, they exposed "normal" male and female mice life-long to UMTS-type RF-EMF. The results show no harmful effects of exposure on fertility and development of the animals.
In summary, the results of these studies do not indicate harmful effects of long-term exposure of mice to GSM- or UMTS-type RF-EMFs, even when animals are exposed over several generations.

Christian Bartsch gave a presentation entitled "Divergent Effects of Permanent Exposure to a GSM-like Signal on Health and Survival of Female Sprague Dawley Rats within the same Rooms: Possible Central Role of Month as well as Year of Birth". The results may indicate that biological response patterns to the same type of RF-signal, applied under identical laboratory conditions, not only vary within certain limits (depending on e.g. month of birth) but can be diametrically opposite if the same experiment is repeated over several years.

David L. McCormick reported on the "Use of Experimental Model Systems to Identify Possible Health Effects of Exposure to RF Fields". After the discussion of the current understanding of the possible effects of exposure to RF fields on the risk of cancer and other chronic diseases in the context of the scientific approaches used to generate such data, a promising study outline was presented which will be applied to close the remaining gaps of knowledge. This includes a chronic toxicity/oncogenicity study in which rats and mice (pregnant dams and their litters) will be exposed to GSM and CDMA signals at 3 power levels each; the completion is planned for fall, 2012.

The session was concluded by a presentation given by **Wolfgang Dekant** and entitled "Predictivity of Carcinogenicity Studies in Animals for Human Cancer Risks". He described the process of risk assessment applied to chemicals and pointed out that this procedure is generally suitable for the field of EMF. For chemicals, all human carcinogens identified by IARC also have been shown to cause induction of malignant tumors in appropriate animal studies underlining that, regarding carcinogenicity, animal studies are highly predictive of human cancer. When using the relevant protocols according to guidelines, animal carcinogenicity studies may be even considered as overestimating health risks, since the experimental design using specific exposure conditions (high doses, lifetime application) is conservative.

One focus of the general discussion of this workshop was the use of the term **"Long-term studies"**. It was suggested to better use the term **"lifetime exposure"** instead, since this term is more precise. It is also important to keep in mind that only studies using lifetime exposure are capable of detecting a carcinogenic potential. Although the lifetime of our commonly used rodent models, rats and mice, are much shorter in absolute time compared to the human situation, they are still valid models, since e.g. repair mechanisms outweigh these differences. The current use of the term "long-term studies" is imprecise, since it subsumes many study types, some of them addressing completely different endpoints. For example, multigeneration studies would certainly be long-term studies, but they are designed to detect adverse effects mainly on fertility and developmental endpoints. However, animals in this type of studies will never reach an age that would allow detection of carcinogenic effects with sufficient certainty. This situation is also not changed if more than two generations (as normally applied in the case of testing chemicals) are added to the study design.

In the further discussion it was agreed that the safe application of experimental data to identify human health hazards requires both the generation of an experimental data set that is relevant to the disease

processes being studied, and an objective analysis of the strengths and limitations of the model system in which those data were generated. Important considerations in this evaluation include:

- relevance of the biology of disease in the experimental model to the human disease
- relevance of the exposure metrics used in the experimental study to human exposures
- sensitivity of the experimental model to disease induction
- magnitude and statistical significance of effects observed in the model system
- level of confidence that the experimental model will accurately predict human responses.

The mainly negative results of the presented studies are in accordance with the vast majority of epidemiological and other animal studies where no harmful effects of RF-EMF exposure could be identified.
For a sound interpretation of the studies, however, some basic information is urgently required. This includes the availability of **good dosimetric models** of both experimental animals as well as humans. Different (early) developmental stages are of special importance for a more scientifically based extrapolation from animal data to the human situation.
It is also considered important to collect as many relevant information as possible to characterize the worst case exposure scenario in humans, both for base stations and the use of cell phones in order to better extrapolate the results.

Based on the approach used for testing and registration of chemicals, pesticides and pharmaceuticals, an attempt was made to modify this procedure and apply it for the safety assessment of EMF.
Since the absence of a risk cannot be proven by theoretical reasons, a pragmatic approach would be to agree on an "acceptable risk". This implies that a set of (valid) studies would be defined beforehand. Based on the results of these studies (and keeping in mind the human exposure scenarios) a comprehensive risk assessment can be performed and appropriate safety factors can be determined. If the whole spectrum of studies does not show any adverse effects, then again (based on the experience with chemicals and pharmaceuticals) this indicates the (relative) safety of the exposure. As a result of this, the circumstances can be defined, under which the situation in humans can be regarded as safe.
If such an approach is used, the following should be kept in mind:
When performing animal studies on potential adverse effects of EMF, energy is added to biological systems. As a consequence of this, any addition leads to thermal reactions in animals, and there is no real "athermal" range. So even if the origin of an observed effect is thermal, it is still relevant for risk assessment if its occurrence cannot be excluded in man. This means that the differentiation between thermal and athermal effects is highly interesting from an academic point of view, but must be approached from a pragmatic point in terms of testing and risk assessment.
Based on these considerations, it should be possible to perform a scientifically based risk assessment for the exposure to EMF, analogously to the one that was proved for the registration of chemicals and pharmaceuticals.

IN VITRO-EXPERIMENTS AND RF
Chair & Rapporteur:
Kenneth R. Foster

Matthias Gaestel (Institute of Biochemistry, Hannover Medical School) presented a review “Monitoring The Effects of Mobile Phone Radiation by the Cellular Stress Response and by Overall Gene Expression Analysis - Recent Approaches and Challenges”. He reviewed studies on effects of RF fields on cellular stress response and gene expression. He noted that many studies that reported effects of RF energy exposure on heat shock proteins suffer from a range of technical problems, and are, in his words, “inherently problematical.” He noted, however, that heat shock response can be used for both detecting and excluding thermal effects of RF-EMF on biological samples. He proposed that future studies should search for non-thermal biological effects of RF-EMF using “omics” techniques (genomics, proteomics). However, he pointed out, “omics” studies are prone to produce false positive results [because of the many different endpoints that are typically compared in such studies] and need to be independently confirmed.

Rony Seger (Weizmann Institute of Science, Israel) presented a paper entitled "Mechanism of Short-Term ERK Activation by Electromagnetic Fields at Mobile Phone Frequencies". He reported his group's study on the effect of RF-irradiation on MAPK (mitogen-activated protein kinase) cascades in serum-starved rat 1 and HeLa cells. The study exposed cells to RF energy (875 MHz, incident field intensity ranging from 0.1-0.3 mW/cm^2). The exposures led to activation of ERK (extracellular-signal-regulated kinase) MAPKs but not stress-related MAPKs. He considered this effect to be nonthermal and "demonstrates a detailed molecular mechanism by which electromagnetic irradiation from mobile phones induces the activation of the ERK cascade and thereby induces transcription and other cellular processes".

In the lengthy discussion that followed his presentation, several members of the audience inquired about the exposure assessment in the study. The exposure was produced by placing the samples in the near-field of a mobile base station antenna that had been placed inside an incubator, with no calculation or measurement of SAR. Other members of the audience inquired about the temperature control inside the sample, noting the difficulty of maintaining accurate temperature in an incubator when a heat source is operated inside it and about the possible biological significance of the results. In response to questions, Dr. Seger stated that the exposure chamber had been developed by a qualified consultant, and he acknowledged that the health significance of his results are unclear at this point.

Magnus S. Jäger (Fraunhofer Institute for Biomedical Engineering), in his paper "Thermal And Non-Thermal Effects Of Shortwave Radiation In Single-Cell Applications" described work by his group on manipulation of cells by relatively intense RF fields. This work has extensive applications to biotechnology, through the ability to manipulate individual cells in small structures, but Jäger did not claim that it had particular relevance to biological effects of RF energy in humans at ordinary exposure levels.

Jan Gimsa (Univ. of Rostock) reviewed elementary biophysical models for polarization and mechanical forces on cells in external electric fields, which lead to a variety of easily measured mechanical responses of cells, typically when exposed to high field strengths (tens of volts per mm) at frequencies in the MHz range and below. He noted that the classical models for such effects assume that the cell membranes are electrically homogeneous. In his talk he considered the possible effects that might occur if the membrane were strongly anisotropic in its electrical properties, with different permittivity and conductivity in directions parallel or perpendicular to the membrane surface. He showed that strong anisotropies, corresponding to a seven order of magnitude variation in membrane conductance, and three order of magnitude variation in permittivity in directions normal vs. parallel to the cell surface, can lead to large changes in the induced dipole moments of the cells at MHz frequencies. He concluded that effects of anisotropy at the level of the cell membrane probably exist but are hidden in the relaxation properties of the cells, and that "hidden anisotropy dispersions" in cell membranes might lead to erroneous interpretation of data. He also noted that the dissipation of electrical energy in different layers of the cell membrane can be as much as ten times higher than in the membrane as a whole.

Markus Antonietti (Max Planck Institute of Colloids and Interfaces), In his paper, "Microwave Absorption of Emulsions Containing Aqueous Micro- and Nanodroplets" described dielectric studies that his group performed on oil-in-water (O/W) and water in oil (W/O) emulsions. He reported on a series of dielectric studies on W/O emulsions (micron-sized droplets of 0.25-4M NaCl or other electrolyte, suspended in a nonconductive low permittivity medium such as oil). The suspensions show a dipolar dispersion in the low-GHz frequency range, below the main dispersion frequency (20 GHz) for pure water. Correspondingly, the loss density of the suspended water was as much as 2000 times higher than that of bulk water at 2 GHz frequencies. He concluded that this was a physical effect associated with high ionic polarization at interfaces inside the suspended droplets, with a shift in the dipolar dispersion frequency of the suspended water compared to bulk water.

Antonietti suggested that the effect might be useful for processing of foods by microwaves, but did not claim that the effect had any biological significance related to possible health risks of microwave energy in humans.

General Discussion

The sessions of invited speakers were followed by a long general discussion. The discussion was introduced by Gerd Friedrich, head of FGF, who asked the audience "what are the open questions – where can we give recommendations, make contributions [to this issue]"? The discussion was led by **Bernard Veyret** (Bordeaux).

In the wide-ranging discussion that followed, members of the audience expressed a number of different points of view. There seemed to be general agreement that more research is needed in the following broad subject areas:

- improvement in exposure assessment/dosimetry to support epidemiological studies,
- potential effects of long-term exposure on humans, and
- effects on potentially sensitive sub-populations such as children and pregnant women.

Several speakers called attention to specific research needs. One participant mentioned the need for micro-dosimetry (in particular, determining the SAR in particular parts of the brain from use of mobile phones and communicating this information to the public). Another participant mentioned the need to confirm the *in vitro* results on ERKs reported by Rony Seger, but using improved and better characterized RF exposure systems. Another speaker mentioned the need to identify systems that had high sensitivity to small temperature changes.

A long discussion occurred about the suggestion, in a report prepared by the U.S. National Research Council, of using neural networks as a test model for possible bioeffects of RF energy. One member of the audience expressed skepticism about the idea, on the grounds that it would be exploratory research ("a fishing expedition") not motivated by a clear hypothesis. In the absence of that, the studies would not address any clearly defined biophysical question, and the same time they could not be interpreted in terms of possible health significance. However, other members of the audience expressed the view that the proposal was a good idea that is worth pursuing.

A short discussion was held on the question: are children more sensitive to effects of RF energy than adults? One member of the audience said that no general statement could be made about age-dependent sensitivity to toxic agents: children could be more or less sensitive to toxic substances than adults, depending on the substance. However, as a precautionary measure, he suggested that children should be assumed to be more sensitive to effects of RF energy until proven otherwise. Veyret called attention to a 2008 ICNIRP statement that there is lack of sufficient evidence to conclude firmly about the relative sensitivity of neonates or juveniles to RF energy compared to adults, and he noted the difficulty of doing research with children as subjects.

One Rapporteur (Foster) came away from the meeting with the sense that scientific results discussed at the meeting did not provide useful guidance for designing further experimental research on possible health risks from RF energy exposure at low (below ICNIRP guidelines) exposure levels. While participants at the meeting discussed a variety of research needs, they were mostly supported by statements of what we do not know (for example, about possible long-term effects in adults or children from long-term exposure to RF energy from wireless communications), rather than statements about a need to follow up any particular research findings that were discussed during the meeting.