Session 1P4
Recent Advances in Bioelectromagnetics Research on Mobile Telephony and Health

Recent Advances in Bioelectromagnetics Research on Mobile Telephony and Health—An Introduction

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Abstract—It is not widely known that biological and health effects of radiofrequency (RF) energy have been studied for about 50 years. Currently, there are about 1500 published studies related to RF health research, covering various disciplines from biophysics to epidemiology, usually defined as bioelectromagnetics research. All these studies can be found at WHO EMF database (http://www.who.int/peh-emf/en/). Current international EMF safety guidelines, established by the International Commission on Nonionizing Radiation Protection (ICNIRP) and IEEE, are based on this extensive research database.

Recent advances in multidisciplinary bioelectromagnetics research addressing mobile telephony and health issue have significantly increased our knowledge about fundamental scientific questions in this area. Improved dosimetry and exposure design have made it possible to conduct well-controlled biomedical experiments. Several carefully conducted theoretical biophysical analyses have also increased our understanding about the responses of cell macromolecules to RF energy. However, inconsistent molecular biological findings have raised questions whether the observed changes are real and whether they have any significance on human health. In this regard, part of the biomedical research community has forgotten a fundamental rule that an observed effect cannot be considered established if it has not been independently replicated and confirmed by other researchers. RF energy—cancer link has been rejected by recent carefully conducted animal studies. However, inconsistent epidemiological findings and misinterpretation of epidemiological data continue to create confusion in mobile telephony—cancer debate in many countries. Studies on other health endpoints than cancer have not either been able to confirm any adverse health effects in humans, such as effects on central nervous system (CNS) at low RF exposure levels. The weight of scientific evidence shows that RF energy does not cause adverse health effects in humans below the internationally accepted RF exposure guidelines, such as established by ICNIRP and IEEE.

1. Introduction

By the end of year 2005, it has been estimated that there will be about two billion mobile subscriptions, and by the year 2010 the amount will increase up to about three billion. Huge advances have been made in the research and development in the wireless communications technology during the past two decades. However, the rapidly increased use of mobile phones and establishment of mobile base station networks has led to concerns that RF energy could possibly cause some unexpected adverse health effects in humans. It has been suggested, for example, that mobile phone use induces brain tumors or promotes brain cancer development, or have other unknown effects on central nervous system. These concerns have led to extensive media debates and also—sometimes—hasty sciencepolitical decisions to initiate extensive biomedical research programs in several countries around the world.

There has been an extensive research effort to investigate the effects of RF energy on human health. The research has been ongoing for about 50 years and has produced a large database, such as the one coordinated by WHO EMF project. When analyzing this extensive research database, it is essential to understand what the weight of scientific evidence tells us about biological and health effects following RF exposure instead of looking at outcomes of single studies. The objective of this paper is to summarize the current research conclusions related to bioelectromagnetics research on mobile telephony and health. This review will not cover all the research findings in detail but will highlight three important questions: 1) is RF energy from mobile telephony able to cause cancers in humans; 2) is RF energy from mobile telephony able to cause adverse effects in human central nervous system; 3) are so-called "non-thermal" biophysical interactions possible at mobile telephony frequencies.

2. The Radiofrequency (RF) Database

The WHO database on biological and health effects of RF energy is extensive and global. It comprises more than 2500 scientific publications from countries around the world. About 1000 of these are reviews, engineering studies and non-peer-reviewed articles. As shown in Table 1, almost 1500 published papers in the database

satisfy criteria for use as a basis to assess the possible public health impacts of exposure to RF fields. Table 1 shows the number of entries in the database for each of the following types of scientific studies on RF fields: epidemiological, human, animal, and cellular studies. In addition, there are about 300 studies are estimated to be published in the near future including 213 ongoing studies and 90 reported-but-not-published studies.

Although all peer-reviewed studies in the RF database (Table 1) are considered relevant to the mobile phone issue, there are also a large number of studies in this database related to mobile telephony frequencies as shown in Table 2. In this table, the number of studies in each of the four types of scientific investigations is shown. There are 673 studies listed in the database using mobile telephony-specific signals, and 412 of these have been completed. All of the literature in the RF database is available to the public on the WHO website shown in Tables 1 and 2.

Table 1: Peer-reviewed papers describing biological and health effects of RF exposure.

- ***All studies are listed on the WHO web site under "citation listings":*** http://www.who.int/peh-emf/research/database/en/

Research Study Type	**Ongoing**	**Reported but not Published**	**Published**
Epidemiology	39	7	215
Human Studies	61	18	139
Animal Studies	54	33	717
Cellular Studies	59	32	376
Totals	**213**	**90**	**1447**

Table 2: Mobile telephony relevant studies in the WHO database.

- ***These studies are listed on the WHO web site:*** http://www.who.int/peh-emf/research/database/en/

Research Study Type	**Ongoing**	**Reported but not Published**	**Published**
Epidemiology	34	5	64
Human Studies	57	17	82
Animal Studies	47	23	170
Cellular Studies	52	26	96
Totals	**190**	**71**	**412**

3. RF Energy and Cancer

Today there seems to be a some kind of overreliance on what can be expected from epidemiological studies. This has particularly become evident when epidemiological studies related to mobile telephony and health have been misinterpreted in massmedia. It is often falsely interpreted that correlation between two factors, such as mobile phone use and cancer, means also that there is a cause-effect relationship. This relationship does not appear plausible when analyzing critically scientific data, both qualified epidemiologic and laboratory animal data.

Recent reviews of the published epidemiology studies [1–3] have not been able to establish a link between RF exposure and cancer. Many of the epidemiological studies have had serious problems in experimental design and exposure assessment. More reliable data will be available when a current large multi-centre case-control study (INTERPHONE), directed by the International Agency for Research on Cancer (IARC), will be completed during year 2006. The weight of evidence from the epidemiological studies indicates no adverse health effects and this conclusion is strongly supported by results from long-term animal cancer studies, many of which have well-defined RF exposure data useful for risk analysis [4]. The weight of scientific evidence of the long-term animal cancer studies indicates no effect on survival or body weight at exposure levels less than 4 W/kg, which is regarded as the exposure threshold for adverse effects in animals. These results provide strong evidence that

RF exposure does not cause life shortening diseases or general toxicity at exposure levels within ICNIRP limits which are set well below the adverse effect threshold of 4 W/kg [4].

A large amount of research has also focused on possible genotoxic effects in vitro following RF energy exposure although it is widely accepted that RF energy quanta are not capable of causing molecular damage in cell macromolecules, such as in DNA. Vijayalaxmi and Obe [5] have reviewed the scientific literature pertaining to the genotoxicity of RF energy in somatic cells, with the specific endpoints of DNA strand breaks, chromosomal aberrations, micronuclei formation, and sister chromatid exchanges. From their examination of 53 studies, the authors conclude that the weight of evidence shows that RF EMF is not genotoxic, and that many of the studies reporting positive results may have had experimental deficiencies. Meltz [6] has reviewed studies focusing on cancer-related bioeffects in mammalian cell systems and concludes that the weight of evidence available indicates that, for a variety of frequencies and modulations, low RF energy exposure levels do not cause genotoxic effects.

The bioelectromagnetics science community has also intensively debated whether RF fields are capable of causing other specific molecular biological effects than genotoxic which could be related to cancer. Main focus has been on the reports claiming that RF energy is able to interfere with the heat shock protein (HSP) metabolism [7]. It has been speculated that the reported effects are due to "non-thermal mechanisms". However, the explanations have remained vague because of lack of plausible biophysical interaction mechanism explaining the molecular biological effects which have not either been successfully replicated in other laboratories [8]. Cotgreave [9] concludes in his review paper that issues concerning the risks to human tissues from RF emissions in vivo are still clouded by a number of inconsistencies and controversies in the literature with respect to HSP response, which must be clarified by novel research. Moreover, the use of high-throughput screening techniques (HTST) such as proteomics or transcriptomics to "identify possible molecular targets" of RF energy are still very immature and are currently not useful for RF health risk assessment.

4. RF Energy and Central Nervous System

Intensive discussions—both scientific and non-scientific—have been ongoing about the potential effects of mobile telephony signals on human central nervous system. It has, for example, been proposed that RF exposure alters important physiological functions in the brain such as brain electrical activity, sleep and blood flow [10, 11].

In a review by D'Andrea et al., [12] the authors conclude: ... "the diverse methods and experimental designs as well as lack of replication of many seemingly important studies prevents formation of definitive conclusions concerning hazardous nervous system health effects from RF exposure. The only firm conclusion that may be drawn is the potential for hazardous thermal consequences of high-power RF exposure."

It has also been proposed that mobile phones may affect the human cognitive performance [13, 14]. However, replication studies with improved methodology [15], including better statistical design, have failed to replicate the original findings. An important methodological point appears to be inclusion of sufficient amount of subjects in the experiments to avoid false positive data when a large number of psychophysiological endpoints are investigated.

It has also been speculated that children with still a developing nervous system would be more vulnerable to RF emissions from mobile phones. This is not supported by scientific facts. From the exposure point of view, carefully conducted theoretical dosimetry studies have shown that there is no evidence for a correlation between energy absorption and head size [16, 17]. Other factors such as shape of the head, tissue distribution and antenna position are more important factors affecting specific absorption rate (SAR). "Child issue" is not either supported by biomedical evidence. Recent well-designed human experimental studies have found no significant differences in cognitive performance as measured by reaction time and accuracy in children exposed to RF fields typically used in mobile telephony [18, 19].

5. RF Biophysical Interaction Mechanisms

The bioelectromagnetics science community has for several years debated whether there would other RF biophysical interaction mechanisms than thermal. Unfortunately, even fundamental research findings in this field are often overlooked in speculative debates. A thermal mechanism depends only on the amount of energy absorbed and thus its frequency dependence is predictable. The amount of energy absorbed will depend on the electrical properties of the tissue and the geometrical interaction with the biological object, both of which will cause well-established frequency variations. There is no modulation dependence for a thermal mechanism. A non-thermal mechanism, on the other hand, would be expected to exhibit frequency dependent responses, modulation dependent responses or both. The current 400 mobile telephony studies cover a wide range of frequencies and modulations and do not support the hypothesis that there is frequency dependent or modulation

dependent response. This conclusion is further magnified by several biophysical analyses and reviews showing that other biophysical mechanisms than thermal are not plausible at mobile phone frequencies.

Foster and Repacholi [20] have concluded: "Modulation introduces a spread of frequencies into a carrier waveform, but in nearly all cases this spread is small compared to the frequency of the carrier. Consequently, any nonthermal (field-dependent) biological effects related to modulation must result from interaction mechanisms that are fast enough to produce a response at radiofrequencies. Despite considerable speculation, no such mechanisms have been established. Existense of "non-thermal interactions at radiofrequencies are not either supported by rigorous biophysical analyses of Pickard [21] and Adair [22].

A special target for discussion has been the DNA molecule and whether RF energy would be capable of causing vibrational modes in this macromolecule and thereby leading, for example, to molecular damage. Even fundamental physics shows that this mechanim does not appear plausible since the RF photon quantum energy is far too low to cause breaks in chemical bonds and/or conformational changes in macromolecules such as in DNA and proteins. Prohofsky [23] has shown in a theoretical study that that absorption of RF energy below several hundred GHz would not be resonantly absorbed into an intramolecular mode for macromolecules such as DNA. The absorption would be into bulk modes of the material in which the molecule is embedded. The thermalization of the RF energy would be primarily to this bulk material, rather than to a single molecule.

6. Conclusions

The weight of scientific evidence of the epidemiological and long-term animal cancer indicates that long-term RF exposures do not induce tumors or promote cancer development. Studies on other health endpoints than cancer have not either been able to establish any adverse health effects in humans, such as effects on central nervous system (CNS) at low RF exposure levels. Theoretical biophysical studies to date and lack of replicable biological effects strongly suggest that the only plausible interaction mechanism at mobile telephony frequencies and emission levels is thermal. The weight of scientific evidence shows that RF energy does not cause adverse health effects in humans below the internationally accepted RF exposure guidelines, such as established by ICNIRP.

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RF Interactions with Biological Molecules and Processes: Quantifying Thermal and Non-thermal Mechanisms

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Electromagnetic fields can have direct effects on mobile ions, atoms, and molecules within mechanis-m-specific constraints for field strength, temporal scale, and spatial dimensions. Threshold conditions for several mechanisms can be estimated from the field magnitude, frequency, and modulation that might satisfy criteria for biophysical interactions of potential physiological significance. The vast parameter space over which technological devices operate indicates the need for fundamental approaches that could apply to many of the established and speculative biophysical mechanisms.

Temperature is a fundamental parameter of biochemistry. It also is the most comprehensive and best-established measure for effects on whole organisms and small regions of tissue. "Microthermal" effects occurring over small distances and lasting brief times have been proposed as a way to focus heating at microscopic and molecular scales. However, thermal diffusion limits temperature changes over cellular dimensions to $\approx 10^{-12}\,K$, even for the extremes of exposure obtainable with common devices. For many years, laboratory reports of differences between the biological effects of CW vs. pulsed and amplitude-modulated RF have stimulated interest in modulation-dependent mechanisms. Heating, which is proportional to E^2 or H^2, is inherently non-linear and could be a basis for some demodulation of pulsed or amplitude modulation at low rates, but the controversial effects reported with definitively non-thermal exposures require other mechanisms, particularly above ≈ 1 to 10 MHz where nonlinearities of transmembrane ionic flux become insignificant [1–3]. The principles of thermodynamics show that various nonlinear interactions between a RF field and a biological system produce characteristic spectral signatures that could be detected by spectroscopy with exceptionally high sensitivity [4]. For example, for a proposed experiment, a detection sensitivity of -127 dBm in an experimental cavity corresponds to ≈ 10 to 100 photons/s/cell at a nonlinearly-produced 1^{st} harmonic [5]. This sensitivity suggests that if harmonic and other frequency signatures of nonlinearity are absent, the nonlinearities of biological matter are so weak that physiological effects are unlikely.

In general, phenomena reported at nonthermal power levels imply the existence of resonant absorption, such as in rhodopsin where a tuned response underlies the high photon efficiency of vision. Similarly, tuned absorption in the RF range would indicate greater sensitivity than thermal absorption, which occurs over a broad bandwidth. Quantitative models and experiment show that such resonances cannot occur below the low-infrared region, particularly because of damping by macromolecular collisions with water molecules [6].

Mechanisms that are inherently statistical, such as stochastically altered binding to DNA, allow estimates for the probability of consequences from the long-term accumulation of rare effects. Assuming an Arrhenius process, even integrating low probability events over years yields so few errors that it would be impossible to detect them against normal background errors.

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Research of Interactions of EM Field and Biological Systems

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Abstract: Paper deals with new results obtained by several research projects in the field of interactions of EM field and biological systems.

1. Introduction: In present time 4 research institutions in the Czech Republic run research projects focused on studies of interactions between EM field and biological systems. In this contribution we would like to give more details about that projects and obtained results —both technical (i. e., developed exposition systems) and biological as well.

Three of that projects (1 in Germany and 2 in Czech Republic) are basic research for simulation of the microwave hyperthermia treatment. Other two project are focused on simulation of the case of exposition by mobile phone.

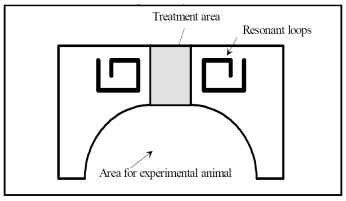

Figure 1: Arrangement of discussed microwave hyperthermia applicator.

2. Applicator for German Project: The main goal of the planned biological experiment is a hyperthermia treatment of the experimentally induced pedicle tumours of the rat to verify the feasibility of ultrasound diagnostics and magnetic resonance imaging respectively to map the temperature distribution in the target area of the treatment. That means to heat effective volume of approximately cylindrical shape (diameter approx. 2 cm, height approx. 3 cm). Temperature to be reached is $41°C$ or more (i. e., temperature increase of at least $4°C$ from starting point $37°C$), time period of heating is 45 minutes.

Considering the necessary effective heating depth for the planned experiments, we have found 915 MHz to be suitable frequency. As an excellent compatibility of the applicator with non-invasive temperature measurement system (ultrasound or NMR) is a fundamental condition for our project, we should have to use non-magnetic metallic sheets of minimised dimensions to create the conductive elements of the applicator. Therefore the applicator itself (see Fig. 1) is created by two inductive loops tuned to resonance by capacitive elements [4, 5]. Dimensions of these resonant loops were designed by our software, developed for this purpose. Coupling between coaxial feeder and resonant loops (not shown in Fig. 1) as well as a mutual coupling between resonating loops could be adjusted to optimum by microwave network analyser.

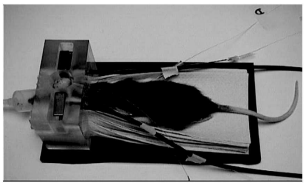

Figure 2: Photograph of the discussed applicator.

The position of the loops is fixed by perspex holder. There is a special cylindrical space for experimental animal in lower part of this perspex holder. As the heated tissue has a high dielectric losses, both loops are very well separated and so no significant resonance in heated area can occur. From this follows, that either the position of the loops with respect to heated area or the distance between the loops is not very critical.

First measurements to evaluate the basic properties of the discussed applicator were done on agar phantom of muscle tissue:

- evaluation of basic microwave properties (transfer of EM energy to the ?
- evaluation of compatibility with US and NMR,
- calculation and measurement of SAR and temperature distribution and its homogeneity.

An Initial Approach to *in Silico* Bioelectromagnetics for RF Exposures

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Introduction. Our group has developed an initial capability for creating and solving single cell and multicellular models that involve interactions with nonionizing electromagnetic fields from essentially dc to ∼2 GHz, and estimates of biochemical change. Interactions can range from weak (e.g., animal navigation, environmental exposures at power line frequencies) to strong (e.g., some telecommunication waveforms, conventional and supra-electroporation with potential medical applications). **Methods.** Our approach involves interactions on multiple spatial scales (e.g., molecules and membranes, cellular organelles, single cells, multiple irregular cells in close proximity, tissue level and whole body) and temporal scales of ns to hours [1–5]. The biological system models consist of a large number of interconnected models. The purpose is estimating field-induced biochemical change, using local models for candidate biophysical mechanisms that couple the field to ongoing biochemical processes. *In silico* (computer-based) assessments can provide rapid, approximate information for large numbers of exposures with different magnitudes and waveforms, a capability partly analogous to high throughput screening. **Results.** We have achieved an initial modeling/screeing capability that is applicable at the multicellular, cellular and subcellular levels. Solutions to a biological system model: (1) describe the microscopic field redistribution due to the applied field (microdosimetry), and (2) estimate the biochemical change due to biophysical mechanisms assigned within the system model. Our microdosimetry models can be combined with anatomic whole body models developed by others for macrodosimetry (typically ∼ mm scale) in humans and laboratory animals. This approach can aid the design and interpretation of experiments involving biological effects of nonionizing electromagnetic fields ranging from dc to microwave frequencies. This provides the possibility of preliminary exposure assessment for many different waveforms *in silico*. The estimated biochemical change due to a particular electromagnetic field exposure is based on known biophysical mechanisms (presently heating, voltage-gated channels and electroporation; others can be added). This allows competing in uences to also be considered quantitatively with initial testing of a hypothesis that a particular biophysical mechanism might cause a biological effect [6]. **Support.** NIH grant RO1–GM63857 and a AFOSR/DOD MURI grant on Subcellular Responses to Narrowband and Wideband Radio Frequency Radiation.

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FDTD Calculations of Specific Energy Absorption Rate in a Seated Voxel Model of the Human Body

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Finite-difference time-domain (FDTD) calculations have been performed to investigate the frequency dependence of the specific energy absorption rate (SAR) in a seated voxel model of the human body. The seated model was derived from the anatomically realistic voxel phantom NORMAN in the standard standing position with arms to the side. Exposure conditions studied were vertically polarised plane-wave electromagnetic fields between 10 MHz and 3 GHz. The frequency range chosen incorporates the whole-body SAR resonance region. The resolution of the voxel model was 4 mm for frequencies below 100 MHz and 2 mm for those above this. Additionally, the 4 mm and 2 mm calculations were overlapped in the 100 MHz to 300 MHz range to investigate the dependence of SAR on voxel resolution. A reduction in the voxel size from previous work at 4 mm allowed the whole-body SAR to be calculated at these higher frequencies.

SAR values are presented as a function of frequency. Results show that the whole-body SAR resonance peak for the seated adult model occurs at a higher frequency and is less well defined than that of the standard standing adult phantom. Additionally, in the sitting posture a second, smaller resonance peak is found to occur at a slightly higher frequency than that of the main resonance condition. Layer absorption plots and images of SAR absorbed in individual voxels demonstrate the way in which the body, when in a sitting posture, absorbs the incident electric field at these frequencies.

Use of Anatomically Correct Head Models and Higher Dielectric Values to Study SAR Difference between Children and Adult's Head and Eye Tissues

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The increasing use of mobile communication devices, especially mobile phones by children, has triggered discussions whether there is a larger radio frequency (RF) energy absorption in the heads of children compared to that of adults.

There have been many studies investigating SAR in child and adult heads using various exposure scenarios and head models. Most of the researchers investigating SAR in the head of adults and children have used down-scaled adult head models to represent the child head. Use of down-scaled head models in the calculation of SAR and temperature has been criticized frequently indicating that a down-scaled adult head model cannot reliably represent a child head when investigating the RF energy distribution. All of those studies have assumed the same value for dielectric parameters in child and adult head models. These are criticized in scientific communities by many researchers commenting that, children organs are not fully developed, they differ not only from anatomical point of view but also their tissue composition is different, with higher water content. Therefore, use of down-scaled head models and same dielectric values may give rise to incorrect exposure assessment and misleading conclusions in terms of health risk assessment.

The aim of this presentation is:

- To compare SAR in 4 different anatomically correct MRI based head models using the same dielectric values for all models.
- To compare SAR in 3 different anatomically correct MRI based head models when the dielectric values are increased from 5 to 20%.

A series of FDTD simulations were carried out to study the localized volume-averaged SAR distribution in 4 different MRI based head models.

The main finding of this study is that the distance of antenna from the exposed tissue, tissue composition and anatomical differences between head models can explain differences in the RF energy absorption between anatomically correct MRI-based adult and child models. In the case of eye region exposure, both anatomical parameters and tissue composition differences between the models affect the calculated SAR levels. Moreover, the results show that the head size does not appear to be a key parameter in the near-field RF exposure. In summary, there is no systematic difference in the RF energy absorption between anatomically correct MRI-based child and adult head models.

Increasing conductivity or both conductivity and permittivity at the same time would not necessarily cause an increase in SAR. In many cases the SAR decreases. Same increase in dielectric value would not cause same SAR variation in different models (individuals). The SAR variation because of increase in dielectric values is very much dependent on the anatomy and tissue layer composition of the exposed region.

Overview of RF Genotoxicity Research

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One of the major issues in the area of electromagnetic field bioeffects is whether or not radiofrequency radiation, in the range of frequencies being used in wireless technologies and mobile/cell telephones, is genotoxic. While there have been a number of reviews, including those which present relative numbers of positive versus negative results, one of the most extensive reviews was that published in December, 2003 [Meltz, M. L., "Radiofrequency Exposure and Mammalian Cell Toxicity, Genotoxicity, and Transformation," Bioelectromagnetics 6: S196–S213]. This review went beyond comparing pluses and minuses, and addressed technical deficiencies found in many of the published papers. Genotoxicity has been of significant importance in the chemical and drug industries; positive results observed in validated in vitro assays are a signal to manufacturers (and regulators) that the chemical/drug they are hoping to develop (or which is already in the environment) has at least the potential to cause mutations in cells in vivo. This suggests that the chemical therefore has the potential to be an initiator in the carcinogenic process, although this may or may not lead to a tumor in an animal, and further may or may not lead to a tumor in a person. A positive result in one in vitro assay is never by itself enough to make a decision; in addition, exposure of animal models to gain additional information about tumor formation before making a decision about carcinogenic potential is considered essential. The results of the above listed paper, which examined data from studies up to and including those published in the year 2002, was that the overwhelming weight of the evidence did not support the hypothesis that RF exposures at different frequencies and exposure levels (SARS) caused toxicity, genotoxic (DNA and chromosomal) damage, synergistic interactions with genotoxic chemicals, phenotypic mutations (limited data), or micronuclei (although suggestive evidence indicating the possibility was available at that time). This presentation will extend the genotypic summary to include more recent publications, including those from the REFLEX program, to see if the weight of evidence has been changed or further supported.

Does Long-term Radiofrequency (RF) Exposure of Laboratory Animals Affect Cancer, Survival and General Health

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Objective: To review long-term exposure studies examining whether radiofrequency (RF) energy causes/promotes cancer or affects survival and general health of laboratory animals.

Methods: In three tables, this report summarizes more than 30 studies of cancer in laboratory animals exposed to RF energy published since 1962. The first table indicates whether or not a statistically significant increase was observed in cancer incidence as well as effects on survival and body mass, if reported. For each of the studies, information is provided on animal species (mice and rats), frequency (and modulation), dose rate (specific absorption rate, SAR), exposure conditions, cancer model, number of animals per group and reference. A second table presents the 15 studies in which animals were exposed for 12–25 months. Thus, about 50% of the studies employed long-term exposures of one year or longer in duration; in 13 studies, animals were exposed for 18-25 months. Significantly, 9 publications describe lifetime exposure studies in which mice and rats were exposed for 24–25 months, the average lifetime of these animals. A third table lists the studies by cancer model (spontaneous tumors, genetically-modified animals, chemically-induced tumors, ionizing radiation-induced tumors and models employing injected tumor cells).

Results: Two studies ([1, 2]) reported that RF exposure had a "protective" effect on cancer development but such results are not supported by the overall evidence. Likewise, the results in three papers ([3–5]) describing carcinogenic effects in RF-exposed animals are not supported by the weight of evidence in the scientific literature that includes follow-up studies addressing the effects reported in Chou, et al. and Repacholi, et al.. Three follow-up studies to the Chou, et al. study failed to confirm an association between RF exposure and an increase in cancer incidence ([6–8]). The follow-up investigation of the experiment by Rephacholi, et al., ([9]) by Utteridge, et al., ([10]) used eight times as many animals and four exposure levels (0.25, 1, 2, and 4 W/kg) and did not confirm an increase in tumors. Two studies reported changes that could not be replicated in the same laboratory ([11, 12]).

Conclusion: The scientific weight of evidence in more than 30 long-term cancer studies in laboratory animals shows no adverse effect of RF exposure up to two years in duration at dose rates up to 4 W/kg on 1) survival, 2) body mass, an indicator of general health status, and 3) carcinogenic processes (initiation, promotion and co-promotion).

*Supported by Motorola

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Epidemiologic Assessment of Cancer Risk from Mobile Phone Use: Where Are We?

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Abstract—More than a dozen epidemiological studies have addressed the possible risk of cancer associated with mobile phone use. Overall, the evidence is reassuring, as risk estimates are close to unity and confidence interval relatively narrow. However, most studies have been based on relatively small number of long-term users. When the analysis was restricted to long-term use of mobile phones, some indication of increased risk was found for acoustic neurinomas. Also, effect related to use on the same side as where the tumor was diagnosed could not be excluded. Despite the substantial volume of research some increase in risk cannot be ruled out at the moment. Knowledge could be further advanced by improving exposure assessment rather than increasing the number of case-control studies. Prospective cohort study is a gold standard in epidemiology and would substantially advance our understanding of the possible health effects of radiofrequency electromagnetic fields emitted by mobile phones.

1. Introduction

When new factors (exposures) are introduced or identified that have the potential to affect human health, multidisciplinary evaluation of possible health impact is required. Risk assessment involves hazard identification, exposure assessment and risk estimation. Hazard identification entails discovery of harmful potential, with its possible target for toxicity. Exposure assessment includes describing the occurrence of the agent, pathways and distribution in the population. Risk estimation comprises identification of mechanism of effect and evaluation of dose-response.

In this review, we summarize the findings from epidemiological studies. In addition, weaknesses in published studies are considered and some suggestions for improved assessment given.

2. Methods

We review the epidemiological evidence regarding cancer risk from mobile phone use. The evidence from studies conducted at individual level is summarized by means of meta-analysis, i. e., quantitative synthesis of results by obtaining a pooled estimate from published results. The pooled results is obtained by weighting the individual estimates with the inverse of the variance (obtained from confidence intervals), which is a measure of precision (amount of information). Consistency of results is evaluated by tests for heterogeneity. When heterogeneity is present, a random effects model is used. If no heterogeneity is found, a fixed effects model is used, assuming that all results represent the same global distribution of values. No such assumption is involved in random effects model.

3. Results

In ecological studies, brain tumor incidence and mortality have been related to mobile phone use at population level, without being able to assess if tumors have occurred in mobile phone users or not. Analyses regarding four Nordic countries showed no obvious increase in benign [1] or malignant intracranial tumors [2] parallel with increasing mobile phone coverage. However, in some subgroups including the oldest age groups and incidence of glioblastoma increase during the late 1990's was reported.

A total of 14 epidemiological studies on mobile phone use and cancer have been published by late 2005. Twelve have been case-control studies and they have included a total of more than 5000 cases with intracranial tumors. The total number of exposed cases is more than 1800 (corresponding to exposure prevalence of 1/3). In the two cohort studies the total number of brain tumor cases is much smaller, only 160. A further limitation of the latter has been relatively short follow-up, only one year in the US cohort and three years on average in the Danish study. This review will therefore focus on case-control studies, which also have an additional strength in more detailed exposure assessment.

Overall, there is substantial evidence indicating that (ever or regular) mobile phone use is not associated with the risk of intracranial tumors. The pooled overall OR from all studies is 1.09, 95% CI 0.86–1.38. For

all malignant tumors, consisting mainly of glioma/astrocytoma, the pooled odds ratio from nine studies is very close to unity, with a narrow confidence interval (OR=1.02, 95% CI 0.77–1.37). Pooled odds ratio for benign brain tumors, mainly meningiomas, from eight studies is actually below unity (OR=0.89, 95% CI 0.75–1.06). For acoustic neurinoma (vestibular schwannoma) little indication of risk overall is found based on seven studies.

Eight studies have compared analog (NMT) and digital (GSM) network. Both showed some increase (OR 1.2–1.3), but neither was statistically significant.

Among subjects who have used a mobile phone for at least five years, a slightly elevated risk of borderline significance is found (OR=1.11, 95% CI 0.99–1.26). This was mainly due to acoustic neurinoma (OR=1.5, 95% CI 1.2–2.0). No clear indication of increased risk was found for malignant tumors (OR=1.1, 95% CI 0.9–1.3) or meningioma (OR=0.9, 0.8–1.1).

Ipsilateral use (mobile phone on the same side where the tumor was diagnosed) was associated with some indication of a slightly increased risk (OR=1.4, 95% CI 0.9–2.0)

When the groups with longest cumulative calling time were combined from different studies (using various cut-points), an odds ratio below one was obtained (OR=0.91, 95% CI 0.74–0.60).

4. Discussion

The number of studies conducted and number of subjects included in epidemiologic studies are relatively large. However, quality of evidence should also be considered. Most studies so far have relied on self-reported extent of mobile phone use as principal exposure measure of exposure. However, the limitations of such approach are evident. Whether or not a person is a regular mobile phone user can probably be reliably assessed. Yet, for construction of quantitative exposure-effect relationship, much more detailed information is required. Validation studies carried out indicate that the precision of self-reported use in terms of number of calls or cumulative call duration is only adequate (correlation coefficients between reported and recorded use 0.5–0.7 for both number and duration of calls) [3–5]. Furthermore, there is tendency to systematically overestimate amount of use (reported call duration up to 2–3 times the recorded value). Additional uncertainty arises from the fact that cumulative calling duration is only a proxy measure for the exposure of interest, energy absorbed in the target tissue from the radiofrequency electromagnetic field.

Random error, if non-differential, i. e., similar among cases and controls, is likely to attenuate any effect of exposure and therefore hinder detection of possible association. In addition to random error, systematic error (bias) is likely to affect the results of epidemiologic studies.

No studies have been published addressing possible information bias, i. e., differential error among cases and controls. Typically, recall bias, based on less complete reporting of exposure among controls, tends to overestimate any effect on outcome. In brain tumors, it is possible that the disease or its treatment, or anxiety following diagnosis may affect the recall and cognitive function of cases, diminishing accuracy of reporting. Also, proxy respondents are used more commonly for cases with malignant tumors than controls, which is likely to affect the quality of information.

The results of a recent study conducted in Finland [6] showed that non-participants were less likely to use mobile phone than study participants. This applied to both cases and controls. Selection bias resulted in apparent protective effect of mobile phone use. It may also distort the shape of dose-response.

These methodological weaknesses are inherent for retrospective exposure assessment. Epidemiological risk assessment is unlikely to improve from simply increasing the volume of research. A cohort study where concurrent mobile phone use is assessed would likely achieve substantially improved accuracy. Another advantage would be the possibility to risk of several health outcomes such as disease incidence and mortality (not only cancer, but also neurological, cerebrovascular and psychiatric disease), as well as 'soft' end-points, including symptoms and well-being. However, such study would require resources as recruitment of a very large number of subjects (probably $> 100,000$) is needed with follow-up for at least 10 years.

5. Conclusion

Currently, the factor limiting our knowledge of possible carcinogenic effect of mobile phone use is no longer the volume of evidence, but quality of epidemiological studies conducted. Improved knowledge could be gained by conducting prospective cohort studies, rather than increasing the number of case-control studies.

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Enzymatic Alteration of Rat Brain Chronically Exposed to Low Level Microwave Radiation

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There has been a growing concern among the public regarding the potential human health hazard of exposure to microwave radiation by these appliances. These radiations affect certain growth related enzymes. They are (i) protein kinase C (PKC), a key enzyme involved in the transduction of signals conveyed from membrane receptors to the intra-cellular region of action of hormones, growth factors and cytokines (ii) ornithine decarboxylase (ODC), a rate-limiting enzyme in the polyamine biosynthesis.

Present work describes the effect of low level microwave radiation on calcium dependent protein kinase activity (PKC) and ornithine decarboxylase activity on developing rat brain. Thirty days old Wistar rats were exposed 2 h/day for 35 days at different frequencies. Exposure was carried out in a specially designed anechoic chamber.

After the exposure the whole brain, hippocampus, and hypothalamus tissue were dissected out and used for estimation of PKC and ODC. Radio labeled P^{32} ATP and C^{14} Ornithine were used for estimation of PKC and ODC activity respectively.

A statistically significant decrease in PKC activity was observed in exposed group as compared to their control counterpart. It is notable that activity on hippocampus showed a significant decline as compared to hypothalamus and the rest of the brain. On the other hand a statistically significant increase in the ODC activity was observed. It is inferred that prolonged exposure to these radiation causes significant alteration in the brain tissue, suggesting a transductive coupling to the cytoplasm. These results indicate a possibility that this type of radiation may also affect membrane bound enzyme such as PKC and ODC, which are associated with the cell proliferation and differentiation. It is suggested that the alteration in these enzymes may affect the behavioral pattern as well as learning and memory functions in developing rat.

Investigation of 900 MHz Electromagnetic Radiation for Effects on Permeability of the Blood Brain Barrier

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Statement of Objective: A study was conducted to examine blood brain barrier (BBB) integrity in animals exposed to GSM RF signals. Significant features include use of an exposure system comparable to that employed in an earlier French study (Dr. Aubineau) with associated detailed dosimetry, multiple exposure levels along with positive controls, and a blind experimental design.

Methodology: Exposure rockets were constructed modeling those used in the French study. Each animal, exposed or sham exposed, were acclimated to the rockets over a 3 day period, after which they were exposed or sham exposed to 1.0 or 4.0 W/kg (brain SAR) for two hours using loop antennas similar to the French study. The antennas were calibrated with documented performance values by IT'IS (Zurich, Switzerland). Agreement with data from the original antenna was outstanding for the antennas fabricated for this study. Male Sprague Dawley rats were canulated in the ascending aortic vessel for introducing fluorescently labeled dextran into the brain immediately prior to exposure. The fluorescent dextran (MW of 70 kdal. and 10 kdal.) is labeled with Oregon Green dye with an absorbance/emission maxima at 496/524 nm respectively.

Analysis: Immediately following exposure, animals were euthanized and brains were perfused with ice cold 4% formaldehyde in phosphate buffered saline. Subsequent to in situ perfusion, brains were removed into 4% PBS at 5 degrees C for 24 hours, followed by 48–72 hours in cold 30% sucrose (in PBS). Brains were then quick frozen using liquid nitrogen and kept at -80 degrees C until preparations for histological analyses. To insure the blind nature of the study, preparation of histological samples and fluorescent analyses of brain tissues were performed by Dr. Nissi Varki and Dr. Kelly Doran (University of California, San Diego)

Results: Six animals were used per exposure condition with analyses ongoing. Preliminary results indicate that fluorescence is limited to the vessel walls with no appreciable extravasation into surrounding brain tissue in animals exposed as well as sham exposed to the GSM signal. No differences have been observed in animals exposed to either the 4 or 1 W/kg levels of exposure.

Mobile Phone Use and Health. Self-rated Health, Neurocognitive Function, Neurophysiological Effects Using 900 MHz Wireless Communication Signals. A laboratory-based Exposure Study

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There is a rapid increase in the use of mobile phones and other wireless devices. Does exposure to such wireless devices impact on human health and well-being Even though there have been a number of reports purporting that mobile phone use elicits health complaints, including skin sensation, headache, difficulties concentrating, sleep disturbance, and fatigue among mobile phone users (mobile phones and cancer risks are not the subject of our current research) , findings have been difficult to reproduce. Some studies, however, have indicated effects of radiofrequency fields (RF) on self-reported symptoms, cognitive functions, blood pressure, brain waves (EEC), and sleep while other studies have not been able to confirm initial findings.

There is lack of sufficiently large, interdisciplinary, well-controlled, laboratory-based studies of the possible non-cancerous and short-term effects from GSM 900 MHz wireless communication signals.

In the present study we have assessed short-term self-rated and neurophysiological effects from laboratory controlled exposure to RF (GSM 900 MHz). Each person is his/her own control. Following a night of adaptation, participants are either exposed to a sham or actual 900 MHz exposure situation. Later, they are brought back for a third sham or real exposure night.

The study investigates the impact from GSM 900 MHz wireless signal exposure, using a double-blind set-up. Outcome measures include:

- Self-rated health, symptoms and belief about actual exposure
- Physiological (individual physiological response patterns), including blood pressure, hormones, and EEG, and
- Social (stress induced through tests during the exposures)

The study is ongoing. All exposures are expected to be completed by February, 2006, and the final report is due late fall 2006.

The study will offer us a better understanding whether day-time phone use is associated with changes in self-rated health, hormonal pattern, mental and cognitive functions as well as night-time sleep and related functions.

The study was approved by the ethical committee at Uppsala University.