Report from a Workshop on:

„Biological and Biophysical Research at Extremely Low- and Radio-Frequencies: (1) Application of Research Results across the Frequencies and Modulation Schemes of Present and Future Wireless Technologies, and (2) Demodulation in Biological Systems"

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Brief Summary

Do similar biological effects occur over the range of frequencies and modulation types used in modern wireless communications, or do particular signals have unique biological effects? Rapid technical change in wireless communications and ever-wider human exposure to its radiofrequency (RF) fields add urgency to this long-standing question about the nature of biological effects of RF exposure. The ability to apply biological research information broadly, rather than requiring specific testing for each signal type, has been called "portability". The workshop addressed 1) whether biological systems respond to modulation of an RF field, 2) whether the results of research on ELF fields relevant for RF fields modulated at ELF, and 3) whether results obtained with one modulation scheme relevant for others. The international group of scientists at the workshop shared an understanding that the key to portability lies in the mechanisms of interaction between RF fields and biological systems.

To establish portability, one research model is to form hypotheses for future biological research on modulation with guidance from mechanisms for the physical interactions of electromagnetic fields with biochemical and biological systems. "Microdosimetry," in the form of biophysical analyses using dielectric theory to quantify effects on biological cells, cell membranes, and subcellular entities, was identified as an important topic in the study of physical mechanisms. For frequencies above approximately 10 MHz, which includes all common wireless communications, there is no evidence that ELF electric and magnetic fields (ELF-EMFs) are produced at biologically significant levels in biological systems as a result of

direct demodulation of modulated RF electromagnetic fields (RF-EMFs). Moreover, the mechanisms for producing biological effects by exposure to an ELF field show lowpass properties, and are not significant at RF frequencies. Consequently, physical principles indicate that the extensive literature from studies conducted at power frequencies (50 and 60 Hz) is not directly portable to RF-EMFs. However, participants noted that research strategies developed from the conduct of ELF-EMF research programs could provide valuable guidance for RF-EMF research.

An alternative RF-EMF research model stresses testing directly for phenomena. This perspective emphasizes epidemiological investigations and studies of laboratory animals exposed to specific device characteristics using specific exposure scenarios. Guidance from physical mechanisms is given less emphasis in favor of answering questions directly from human health experience and laboratory research with animals. Generalizations permitting portability would be drawn from phenomenological databases and secondarily would make use of mechanistic models. Likewise, risk assessments for a particular RF exposure mode would consider the acquired data together with considerations derived from research on mechanisms of interaction. Such research can help determine which parameters of exposure (among an infinite number of possible parameters) are significant. This research model gives little opportunity to avoid a multiplicity of tests for each of the distinct modes of RF exposure, although in time, confidence in the research and interaction models can build sufficiently to permit setting rules for portability.

1. Background and intentions of the workshop

The number and variety of radio technologies have increased dramatically in recent years. In addition to existing cellular telephone systems that use FM, TDMA (e.g. GSM), CDMA, and other modulation techniques, UMTS cellular telephones and Bluetooth devices for local wireless networking and data transmission are prominent among forthcoming technologies[1]. At the same time, there is interest in biological research to assess potential health risks of radiofrequency electromagnetic fields (RF-EMF). However, a prohibitive

[1] FM, frequency modulation; TDMA, time domain multiple access; GSM, global system for mobile communications; CDMA, code domain multiple access, UMTS, universal mobile telecommunications system; Bluetooth denotes a low power, low bandwidth wireless interconnection standard operating over a range of about 10 m.

number of investigations would be needed if each modulation scheme were fully tested in a battery of experiments. A large experimental database demonstrates hazards from acute and chronic exposures only if the body or localized tissues are heated, typically requiring an increase of several degrees. There also is a body of uncertain evidence for biological effects under exposure conditions that, with varying degrees of certainty, do not produce significant heating. Lastly, there are data showing modulation-specific effects, but no direct evidence for hazardous effects specific to modulation. However, the rapid expansion of wireless communications occurs at a time when evaluations of all potential categories of hazard are incomplete and when it appears that exhaustive proof of safety by individually testing all waveforms and devices is not feasible.

The workshop addressed ”portability,“ the transfer of biological research information across the frequencies and modulation types that characterize modern radiofrequency communications. The biological significance of low frequency signal components encoded in radio signals was addressed in light of normal nerve and muscle activity that produces low frequency electrical activity in the body over the range from a few hertz to a few thousand hertz. The workshop examined biophysical and biological information to address the hypothesis that biological systems respond to modulated radio frequency signals through direct demodulation or other mechanisms.

The workshop focused on three main questions:

- Can biological systems respond to the modulation of radio waves?
- Are results from research conducted with extremely low-frequency fields relevant to the RF range (”ELF to RF portability”)?
- Are results from biological research conducted with one modulation scheme relevant for other modulations and other carrier frequencies (”modulation scheme portability”)?

Definitive answers to these questions would permit a more systematic understanding of past and future RF research by leading to a better grasp on the mechanisms of field effects on biological systems. In turn, health risk assessments for present and emerging radio technologies will be more reliable and better received by both scientists and the public.

Forty-two specialists from Europe and United States attended the meeting, which featured lectures from 12 invited speakers and several lengthy discussion periods. The workshop was sponsored by the Forschungsgemeinschaft Funk (Research Association for Radio Applications), in cooperation with the Berufsgenossenschaft für Elektrotechnik und Feinmechanik (Germany), and COST 244bis (a committee of the European Cooperation in the field of Scientific Technical Research that is focused on the biomedical effects of electromagnetic fields).

2. Program and course of the workshop

As an introduction to the many technologies now in use and planned for the near-term, H. Hirsch, Dortmund (Germany), presented an overview of current and emerging technologies for wireless communications, including their signal characteristics and the strength and duration of exposures.

The topic, "Can research results from the ELF area be transferred to the radiofrequency area?" was developed by seven presentations and discussions led by session moderator C. Portier, Research Triangle Park (USA). The speakers and titles of their talks were:

- "Established and proposed mechanisms of interaction at radio frequencies", K. Foster, Philadelphia (USA),
- "Studies on effects of ELF and non-thermal, modulated radiofrequency on biological molecules and sub-cellular fractions", S. Johnston, London (UK),
- "Studies on effects on the level of cells and tissue", B. Veyret, Bordeaux (France),
- "Studies on effects of ELF and non-thermal, modulated radiofrequency on the level of cells and tissues", R. Meyer, Bonn (Germany),
- "Studies on effects of ELF and non-thermal, modulated radiofrequency on the level of animals", A. Lerchl, Münster (Germany),
- "Studies on effects of ELF and non-thermal, modulated radiofrequency on the level of humans", U. Bergqvist, Linköping (Sweden),
- Limits and basic problems in research on non-thermal biological effects of LF and RF-EMF and for detection of demodulated signals in the presence of noise of physiological

origin, M. Swicord, Ft. Lauderdale (USA).

The second major topic, “Can biological systems demodulate radiofrequency signals?” was moderated by C. Davis, College Park (USA) and featured these presentations:

- “Biophysical mechanisms for demodulation”, J. Silny, Aachen (Germany),
- “Non-linearity in biochemical and biological functions; implications for demodulation”, J. Weaver, Cambridge (USA),
- “Membrane models for interactions with modulated fields”, G. d´Inzeo, Rome (Italy),
- “Laboratory studies on demodulation by biological cells and tissues”, W.F. Pickard, St. Louis (USA).

As part of this topic, A. Sheppard, Redlands (USA) led a discussion on a recent result in microdosimetry (calculation of cell membrane RF field strengths) and on the evidence and theory that apply to each of the major types of modulation.

B. Veyret, Bordeaux (France), led the final session in which he presented an overview of workshop ideas and led discussions that examined the value of various theoretical approaches and looked forward to the features needed in future research.

3. Principal ideas from the lectures and discussions

Technical features of current and emerging technologies

A variety of modulation techniques is in use and planned. The number of RF energy sources and the variety in modulation techniques are expected to increase in the future. Some examples are “Bluetooth” devices (using time division duplex division and frequency hopping techniques), digital radio and television broadcasting (using coded frequency division multiplexing and various phase shift modulations in bands), cellular telephony (using pulse, phase, and amplitude modulations for digital systems and frequency modulation for analog systems), wireless devices for computers and entertainment, and collision avoidance radar for automobiles.

Are results from research conducted with low-frequency fields relevant to the RF range?

Most participants felt there was no existing theory that would support the linkage of research findings on ELF-EMF to RF-EMF. No one expressed doubts about the conclusion that exposure to amplitude modulated RF-fields in the frequency range of mobile telephones is unlikely to produce biologically significant ELF electric fields across the cell membrane, or elsewhere in biological systems. This view is based on biophysical theory and a limited amount of supporting experimental data. Consequently, results from biological effects research with ELF-EMFs are very unlikely to have any direct bearing for exposures to RF-EMF.

Are there experimental observations that clearly indicate that modulated RF-fields have specific biological effects in contrast to unmodulated fields?

There are abundant data showing that modulated high-level RF fields have biological effects and that modulation is an important factor (for example, consider the studies on microwave hearing). However, these have no direct bearing on RF signals typically used by communications systems.

Although a number of experimenters have reported effects that depend on amplitude modulation at low levels of RF exposure ("non-thermal" SARs that are below exposure guideline limits set by ICNIRP, ANSI/IEEE and others), the effects remain isolated to particular *in vitro* systems and have not generated models that can be applied to portability across the various types of amplitude modulation. Although a few experiments have been repeated successfully in independent laboratories, others have not, and the question of whether modulation is important for biological effects remains open. Many participants emphasized that established hazardous effects of RF fields of the kinds used in communications systems (pulsed and non-pulsed) are associated only with excessive heating. These and other participants felt the need for further research data specific to modulated RF fields in general and new technologies in particular.

What are the demonstrated and potential mechanisms for demodulation in biological systems?

Several mechanisms were discussed in consideration of the possibility of unique biological responses to amplitude modulation and pulse modulation, which can be viewed as a type of amplitude modulation.

Can biological systems extract a low frequency signal from modulated RF fields? In answer to this basic question, the participants could not identify a biological structure that could demodulate the RF signals used in existing and emerging wireless technologies and thereby produce ELF fields at a biologically significant level. Identified nonlinear interaction mechanisms require responses at the carrier frequency of the field and these decline sharply for frequencies greater than a few kilohertz and become very ineffective at radiofrequencies. RF fields will induce membrane potential changes up to the gigahertz range, but the potential changes are very small above the cell cutoff frequency, which is typically in the low megahertz range. Biological studies show that the maximum frequency at which demodulation can be measured in cell preparations is about 10 MHz, and at that frequency the process is extremely inefficient. A review of biophysical theory and experiments indicated it is highly unlikely that the identified nonlinear interactions in biological systems would produce fields of a biologically significant magnitude by physical demodulation of RF fields induced in the body by low-powered communications equipment.

One idea is that at frequencies above 10 MHz biological structures may support a form of demodulation as a consequence of the observation that biological systems are thermodynamically open, operate far from thermodynamic equilibrium, and are characterized by non-linear dynamic responses. Consequently, it has been suggested that there may be non-linear responses to RF fields. This idea has not been evaluated critically or tested experimentally and therefore remains speculative. In addition, critics have stated that naturally occurring damping mechanisms would prevent non-linear dynamical effects.

There is also a proposal that demodulation might occur because of a direct, time-varying influence on ongoing biochemical reactions. In this case, modulation patterns would be important because rapid variations in RF energy could affect the rates for molecular and supramolecular chemical reactions. For example, reactions involving calcium ions might be affected by sinusoidal or pulsed modulation at ELF frequencies. This speculation has not been developed into a theory that can be subjected to critical review.

Participants felt that frequency modulation (FM), which involves a frequency shift that is a very small percentage of the carrier frequency, is unlikely to change biological responses to RF fields.

How might portability be affected differently by thermal and non-thermal effects?

Although there are different definitions of the terms "thermal", "athermal", and "non-thermal", usually a thermal effect involves an increase in temperature that is biochemically or physiologically significant, for example, by affecting biochemical temperature sensitive reaction rates. Thermoregulatory responses and (at a high exposure level) physiological stress occur when body temperature is increased sufficiently. However, microwave hearing is an example of a thermal effect that occurs with an immeasurably small net temperature increase and depends on the rate of temperature change. At lower levels, "athermal" exposures occur with significant heat flow, and possible thermoregulatory effects, although body temperature changes are small or not detectable. Still lower exposures are "nonthermal" because heat flows and temperature changes are so slight that neither biochemical nor physiological effects are likely to be detectable. At least one member of the panel felt this issue had not been adequately addressed from both experimental and theoretical views and felt there were no clear definitions of what constituted thermal versus nonthermal exposures when dealing with net energy input into a biological system and in consideration of the multitude and complexity of the biochemical reactions in biological systems.

Discussion revealed interest in additional quantitative studies of localized heating and energy transport that occurs without significant temperature gradients. Analyses at millimeter and microscopic dimensions (sometimes called "microdosimetry") are still rare in comparison with macrodosimetric studies of external fields acting on the body at the anatomical level. The temporal and spatial nature of temperature gradients at a microscopic level provoked discussions about whether microscopic "hot-spots" could arise because of differential RF absorption by cell membranes, water layers, and proteins. Participants stated that any such analyses should be undertaken with recognition of severe limitations imposed by the quantitative heat transfer studies first conducted in the 1940s. These demonstrated that the rapid diffusion of heat over micrometer-sized volumes, typical of cells, precludes any meaningful temperature gradients over microscopic dimensions for exposures to RF fields such as those produced by handheld communications devices. No one opposed the statement that qualitative discussions were not sufficient to evaluate the proposal that rapid energy transfer over sub-cellular and molecular dimensions be considered as a possible mechanism for RF field interactions. Some participants emphasized the potential importance of this idea and advocated calculations to address it, but others emphasized doubts that there could be any biochemical or biological interaction in the face of rapid temperature equilibration occurring on the microsecond time scale.

Are investigated modulation schemes relevant for other modulations and other carrier frequencies ("modulation scheme portability")?

There was agreement that this form of portability, which would allow generalizations and extrapolations across modulation schemes, would be supportable only if there were agreement on the accepted mechanisms of interaction of the field with biological systems. At present, only the thermal mechanism satisfies the requirements for portability, and this mechanism does not suggest that modulation plays a role for exposures with comparable average SARs. Thermal considerations indicate that, with two exceptions, results with different modulation patterns are equivalent if their average heating effects are the same. The exceptions occur for high-intensity pulses that can elicit a pulse-dependent auditory response ("microwave hearing") as the result of a small pressure wave that occurs when the brains of exposed subjects undergo sudden thermal expansion, or high rates of change of temperature that can depolarize membranes. This thermal expansion, which requires field strengths that greatly exceed levels produced by the use of wireless devices, produces pressures too low to be anticipated as the cause of adverse effects.

What do we know about mechanisms of interaction of RF-EMF with biological systems?

Resolution of portability issues requires renewed consideration of all possible mechanisms. Thermal effects (and effects presumably thermal in origin) have been studied extensively at anatomical levels in animals and human subjects and in a large number of *in vitro* biological preparations. The common dosimetric measures for microwaves, specific absorption (SA) and specific absorption rate (SAR), are inherently thermal in nature, but discussants noted that temperature is a still more fundamental measurement of thermal effects. Alternatively, SAR and SA also are useful measures of exposure in the absence of measurable temperature change. It also was stated that despite many attempts to devise biophysical models for nonthermal effects, there are none that have been experimentally verified or are free from devastating theoretical criticism. The observation was made that many questions about biological effects of RF energy at the microscopic level correspond to the question of whether RF energy affects biological chemistry, based on recognizing that biochemical changes can lead to biological effects. Temperature unquestionably affects biochemical reactions, but some discussants saw a need for further mechanistic biophysical research into the possibility of alterations of cellular function even if temperature changes are small in comparison with normal fluctuations of body temperature.

Strategies for future research activities to develop scientific data and tools for risk assessments of emerging RF technologies

Based on recognition by workshop participants of a need for more research into biological effects of amplitude modulated (including pulsed) RF fields, there were exploratory discussions on desirable approaches for this research. The principal question was whether research should be driven by hypotheses generated directly from biophysical theory, or if it should be guided by existing reports of biological effects, or based on the classical toxicological screening paradigm for environmental safety assessment.

There was little support for follow-up research on reported biological effects that were difficult to replicate and not supported by biophysical theory. Support for a routine safety assessment was based upon the general concept that establishing safety does not always require hypothesis driven research, but instead can be based on development of a "comfort level" with the data, such as has been established for other environmental agents in a process requiring many years. There was also strong support for hypothesis driven research that could enhance understanding of mechanisms of interaction. Investigations bearing on the coupling of fields to molecular and biochemical events were identified as a promising approach.

A brief discussion presented the idea that high duty rate pulsed fields and amplitude modulation of the type used for spread spectrum communications (for example, CDMA wireless telephony) appear less likely to have biological effects than low duty rate pulses and sinusoidally amplitude-modulated signals. Furthermore, studies with low duty rate pulsed waveforms were thought more likely to be useful than those with sinusoidal amplitude modulation. One speaker suggested conducting biological experiments with different duty factors while holding average power constant.

Consideration of the relative value of research conducted at different hierarchic levels provoked discussions of the different types of information obtained from epidemiological, toxicological, and laboratory investigations. In illustration of this point, it was noted that multicellular systems are capable of greater sensitivity than single cells, although at the sacrifice of response speed. (Examples of this concept can be found in sensory physiology, such as electroreception in certain fish and the highly evolved senses found in animals and man. Electroreception is limited to fields at extremely low frequencies and has no direct relevance to RF bioeffects.) The hierarchical concept suggests a limitation for extrapolations made from data obtained at very low levels of organization. At the other extreme, human studies are limited by practical and ethical constraints on experimentation as well as uncertain interpretation of physiological changes. For example, transient changes in EEG may be a benign biological response, but it is not logically possible to exclude the possibility of a related health effect. Several studies of brain cancer and other diseases among users of cellular telephone handsets have been reported recently and others are in progress. However, it is anticipated that epidemiological studies of persons exposed to RF fields from wireless technologies will not yield firm conclusions in the near future.

4. Conclusions

- At the present time, the concept of a demodulation process producing an ELF-EMF field at a biologically significant level in biological systems exposed to amplitude modulated RF fields used for telecommunications is not supported by either a defensible theory or direct experimental evidence.
- The problem of "portability" of biological effects from one kind of modulation to another can be solved by knowing the relevant basic mechanisms of interaction. This knowledge requires a theory and supporting data.
- Alternatively, portability may emerge by development of a substantial database from phenomenological research on each of several of RF signal types.
- The concept that biological effects of RF energy are caused by heating is well established. This concept supports a degree of portablility among different RF bioeffects studies, and suggests that average SAR (and not specific waveform characteristics) is the major dosimetric quantity of biological significance. However, controversy exists because although heating can explain effects observed for high power levels, it does not appear to explain effects reported at low power levels. There often is controversy about the reliability of such effects because of conflicting data or the absence of independent

experimental confirmation.

- Further research is necessary on the question of whether modulated fields, including pulsed fields, differ in effectiveness in comparison with unmodulated fields.
- Further research on microdosimetry that applies dielectric theory to cells and subcellular entities is needed to achieve a better understanding of the proposal that in the absence of overall temperature change, RF energy might influence biochemical processes over microscopic dimensions and sub-microsecond times. However, existing research on heat transport at microscopic dimensions sets the challenge of how RF energy, which at the microscopic level cannot introduce significant temperature gradients, might be biologically significant.