Workshop

Do sinusoidal versus non-sinusoidal waveforms make a difference?

Abstracts

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COST 281

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CONTENTS

CALL FOR CONTRIBUTION

The role of the signal time course in potential EMF-health effects on Sinusoidal versus non-sinusoidal signals including ultrashort high peak power, and ultra wideband pulses (Short title: "Do sinusoidal versus non-sinusoidal waveforms make a difference?")

COST 281-Workshop, Zurich, February 17-18, 2005

Motivation and purpose of the workshop

Already existing and emerging new technologies make increasing use of nonsinusoidal signals and even ultrashort pulses. This development stimulates the ongoing debate whether specific non-thermal effects should be considered to add to the thermal concept of EMF radiation protection and might lead to more public concern about such new technologies if sound scientific advice is lacking. Specific attention need to be given to pulses with ultrashort rise time and/or duration which probably could induce biological effects on cells and tissues, which are different from those, produced by continuous sinusoidal fields. Are there specific mechanisms, based on processes of fast energy transfer apart of those already known to cause microwave hearing? Is it possible that such kinds of mechanisms could cause non-thermal effects, occurring without measurable temperature increase?
Do ICNIRP limits deserve further development to account for the increasing prevalence of non-sinusoidal and ultrashort high peak as well as wide band signals?

In the proposed workshop the attempt shall be made, to critically review the energy model of interaction and compare results from sinusoidal and non-sinusoidal signals and to learn from experiences of other research projects, irrespective of the fact that strong fields were applied. It should be checked, whether established effects, found at intensities even magnitudes above the ICNIRP exposure limit levels may give hints to potential time course dependent mechanisms at environmental levels.

Modern technology already now makes it possible to generate ultrashort pulses as well as of trains of microwaves with enormous intensities. Recently, the application of extremely high power microwave pulses (EHPP) for military purpose were investigated. Possible new insight in mechanisms could be gained from the use of directly coupled short high-voltage pulses in biotechnology in order to transfer macromolecules into the cell, the so called electroperforation or electroporation of cell membranes, as well as the electrofusion of cells, which have already became routine during the last decades. Shortening the pulse duration from milliseconds down to some tenth of nanoseconds, and increasing its intensity of these pulses, opens new possibilities in biotechnological treatment of cell constituents, such as nucleus and mitochondria.

In spite of the different types of pulses: trains of microwaves on one hand, and more or less rectangular DC pulses on the other hand, of course, the differences of their

physical properties must be kept in mind. When going deeper into the physics and biophysics of their properties, a number of similarities can be found, justifying their inclusion in this workshop. From the biophysical point of view, except for the direct electrostatic interaction of the DC-Pulses with macromolecular dipoles in the cell, a common feature of both types of pulses is the extremely fast process of energy accumulation, and probably also the differences in energy accumulation in molecular or submolecular dimensions.
This workshop should review the state of the art, identify needs for future studies, and discuss potential implications for further development of exposure limits.

Proposed topics of the workshop and schedule

1. **Introduction**: Nonsinusoidal, pulsed and amplitude-modulated fields in technology of mobile phones and other technologies.
2. **Nanosecond ultra wideband pulses in biotechnology.**
3. **Biological effects of modulated versus nonmodulated fields including extremely high power microwave pulses.**
4. **Specific interaction mechanisms of modulated fields including ultrashort high peak power, and extremely high power microwave pulses.**
   (Dielectric response of cell constituents on steeply edged pulses and trains of microwaves)
5. **Aspects of safety standards for extremely high power microwave pulses.**
   Is SAR applicable ?

AGENDA

Thursday, February 17, 2005 ***Room No.***

08:15 – 10:00	**STEERING COMMITTEE MEETING (SCM)**	***F 33.4***
10:00	**Welcome by Gregor Dürrenberger (Research Foundation Mobile Communication)**	***G 60***
10:05 – 12:00	**MANAGEMENT COMMITTEE MEETING (MCM)**	***G 60***
12:00 – 13:00	*Lunch*	***GEP***

WORKSHOP "Do sinusoidal versus non-sinusoidal waveforms make a difference?"

Session 1: Modulation of RF-fields in mobile phones and other technologies. ***G 60***

Welcome and Chair: Norbert Leitgeb

13:00 – 13:30	Werner Bächtold, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland – Mobile communication signals on the air
13:30 – 13:45	Discussion
13:45 – 14:15	Jørgen Bach Andersen, Aalborg University, Denmark – Signal forms in wireless applications
14:15 – 14:30	Discussion
14:30 – 14:45	*Coffee Break* ***Foyer G60***

Session 2: Biological effects of modulated versus nonmodulated fields. ***G 60***

Chair: Maila Hietanen

14:45 – 15:05	Kenneth R. Foster, University of Pennsylvania, Philadelphia, USA – Biological Effects of Radiofrequency Fields: Does Modulation Matter?
15:05 – 15:15	Discussion
15:15 – 15:35	Vijayalaxmi, University of Texas, San Antonio, USA – An Overview of Genotoxic Potential of Electromagnetic Radiation with different modulations in Mammalian Somatic Cells
15:35 – 15:45	Discussion

15:45 – 16:05 Martin Röösli, University of Bern, Switzerland - Waveform specific effects: what can epidemiological studies contribute?
16:05 – 16:15 Discussion

16:15 – 16:30 *Coffee Break* ***Foyer G60***

16:30 – 16:50 Jiri Silny, Aachen University Hospital, Germany – Influence of pulse-modulated GHz microwaves on the excitation of human nerves and muscles compared with continuous wave exposure
16:50 – 17:00 Discussion

17:00 – 17:20 Stanislaw Szmigielski, Military Institute of Hygiene and Epidemiology, Warsaw, Poland – Assessment of immunotropic effects of exposure to pulse-modulated microwave radiation in relation to continuous wave exposure
17:20 – 17:30 Discussion

Cancelled

17:00 – 17:20 Igor Y. Belyaev, Stockholm University, Sweden - Non-thermal biological effects of microwaves: current knowledge, further perspective and urgent needs
17:20 – 17:30 Discussion

19:00 – 23:00 COST Social Event

Friday, February 18, 2005

Session 2 (continued): ***G 60***

Chair: Maila Hietanen

08:00 – 08:20 Peter Achermann, University of Zurich, Switzerland – Pulse modulation appears crucial for RF-EMF-induced alterations in brain physiology
08:20 – 08:30 Discussion

08:30 – 09:00 Discussion on special modulation effects

09:00 – 09:15 *Coffee Break* ***Foyer G60***

Session 3: Biological effects of different kinds of high peak pulses. ***G 60***

Chair: Kenneth R. Foster

09:15 – 09:35 Vladimir Sukhorukov, University of Wuerzburg, Germany – Electro-permeabilization of cells by pulses of high field strength and ultra-short duration
09:35 – 09:45 Discussion

09:45 – 10:05 Andrei G. Pakhomov, University of Texas, San Antonio, USA – Climbing the Megawatt-Per-Gram SAR Peak: The Research Into Bioeffects of Extremely High Power Microwave Pulses
10:05 – 10:15 Discussion

10:15 – 10:35 Gian Piero Gallerano, ENEA, Frascati, Italy - Biological effects of high peak electric field picosecond pulses in the THz region: irradiation studies on human lymphocytes and model cell membranes

10:35 – 10:45 Discussion

10:45 – 11:15 Discussion on high peak pulses

11:15 – 11:30 *Coffee Break* ***Foyer G60***

Session 4: Interaction mechanisms and safety standards. ***G 60***

Chair: Roland Glaser

11:30 – 11:50 James C. Weaver, Massachusetts Institute of Technology, Cambridge, USA – Screening of electromagnetic field exposures in silico

Cancelled

11:50 – 12:00 Discussion

11:30 – 11:50 Iftekhar Ahmed, University of Bradford, UK - Is a square-law junction essential for demodulation of modulated waveforms in tissue?

11:50 – 12:00 Discussion

12:00 – 12:20 Phillip Chadwick, MCL, Newbury, UK – Exposure standards for pulse-modulated fields

12:20 – 12:30 Discussion

12:30 – 12:50 Discussion on mechanisms and safety standards

13:00 – 14:00 *Lunch* ***GEP***

14:00 – 16:00 **MCM** ***G 60***

Microwave Communication Signals on the Air

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The lower Gigahertz range has been invaded in the last two decades by wireless communications applications. The frequency range with lowest man made and natural noise interference is exploited by mass applications. The different air interface standards reflect the various needs from mobile communications to short range communications, control and sensing. The electromagnetic signals show all known modulation schemes and a range of bandwidth and power density. In this talk the main players in the ether are presented, from GSM, UMTS, WLAN to Bluetooth. It is shown, that from the point of view of the compound detectable signals, the statistics of the superposition of many signals has not changed significantly since wide spread introduction of TV-broadcasting.

Signal forms in wireless applications

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Due to technological advances wireless technologies are now penetrating many aspects of life, from communications between people and between devices. Wireless sensors are envisaged to be a major new development, including RFID devices. All these existing and new devices radiate electromagnetic waves, and in all cases there are different aspects of time variations of the power density of the wave. Apart from the actual communication there are many control signals, which are necessary for allowing multiple users on the network, the method of access. The underlying thesis for biological studies is that the signals are demodulated, such that low frequencies are generated, in contrast to the original signal which only has frequencies in the microwave band.

The presentation will attempt in a tutorial way to explain the basis for the power variations for the access technologies and modulation technologies. 2nd and 3rd generation mobile technologies GSM and UMTS, will be treated first with the primary emphasis on the power fluctuations of UMTS due to the spread spectrum character of the signal. This introduces power frequencies in the MHz range, which is a new phenomenon.

Multi-carrier techniques have already been used for some time in the broadcast networks, but is now entering mobile communications, and it is expected that they will be used in future 4th generation broadband systems, with data rates approaching 1 Gb/s. In a multicarrier system many frequencies are used simultaneously, which also creates power fluctuations.

Ultra-Wideband-Systems will also be treated, both in the time domain and the frequency domain.

Biological Effects of Radiofrequency Fields: Does Modulation Matter?

Kenneth R. Foster

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There has been much recent discussion about the relevance of modulation in biological effects of radiofrequency (RF) energy, and its relevance in planning health and safety studies and setting exposure guidelines. In this presentation I consider the possible biological significance of modulation from mechanistic and biophysical perspectives, building on a recent Commentary on the issue* Typical RF communications systems employ complex modulation schemes involving a mixture of amplitude (or pulse) and frequency modulation. With the exception of ultrawideband communications signals, the frequency spectrum of the modulated signal is very narrowly centered about the carrier frequency, with a bandwidth (range of frequencies present in the signal) that is very small compared the carrier frequency. Thus, contrary to statements that sometimes appear in the bioeffects literature, RF communications signals have no "low-frequency" component. However, the frequency spectrum of the power (*not* the power spectrum of the signal) contains low-frequency components introduced by amplitude modulation. The role of modulation in eliciting biological effects from exposure to RF fields depends on the mechanism involved. I will review several well-established nonthermal interaction mechanisms between RF fields and biological systems. These can be either linear or quadratic in the applied field. In principle, a quadratic response could make a biological system responsive to an amplitude modulated waveform even though it is not responsive to the RF carrier itself. However, quantitative analysis indicates that very strong fields would be required to produce observable changes in a biological system through these mechanisms. By contrast, a variety of thermal mechanisms are well established. These are related to the absorbed power and, under appropriate exposure conditions, could lead to modulation-dependent biological effects being observed. The paradox of modulation-dependent biological effects of RF fields is part of the larger paradox of biological effects of RF fields. Despite decades of speculation, no mechanism has been demonstrated by which RF fields, whether modulated or not, can produce biological effects at environmentally plausible exposure levels apart from effects of heating. But there is a scattering of reports of biological effects at exposure levels below present exposure guidelines, some of which appear to depend on modulation. However, the effects are poorly understood and the experiments are frequently open to question on technical grounds. Resolving this paradox can only be done with respect to particular cases. It will require hypothesis-driven studies to clarify the reported effects and understand their mechanisms.

* K. R. Foster and M. Repacholi, Biological Effects of Radiofrequency Fields: Does Modulation Matter?, Radiation Research 162:219-225 (2004)

An Overview of Genotoxic Potential of Electromagnetic Radiation with different modulations in Mammalian Somatic Cells

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A multitude of devices that emit non-ionizing electromagnetic radiation are already in use for a variety of civilian and military purposes. Emerging new technologies are expected to utilize ultra-wideband and ultra-short high peak power pulse electromagnetic radiation as well. In recent years, public attention has been drawn to the possibility that acute and/or chronic exposure to electromagnetic radiation could have adverse effects on human health, including the development of cancer.

There has been a steady increase in investigations determining the potential of electromagnetic radiation (continuous or pulse form) to induce genotoxicity, assessed from DNA strand breaks, chromosomal aberrations, micronuclei and sister chromatid exchanges, in mammalian cells. The importance of conducting these studies comes from the fact that most genotoxic agents are also carcinogens. The results from genotoxic investigations which were published during 1990-2003 in peer-reviewed scientific journals have been reviewed. No evidence for excess gentoxicity was reported in mice exposed to ultra-wideband electromagnetic radiation (Vijayalaxmi et al. Int J Radiat Biol., 75, 115-120, 1999). Among a total of 53 reports which utilized radiofrequency radiation (RFR) the conclusions from 31 studies (58%) did not indicate increased damage to the genetic material in RFR-exposed cells as compared with sham exposed and/or un-exposed cells, while those from 12 investigations (23%) have suggested an increase in such damage in RFR-exposed cells. The observations from 10 other studies (19%) were inconclusive (Vijayalaxmi and Obe. Radiat Res., 162, 481-496, 2004). It is interesting to note that in some of the above studies significant differences, between the cells exposed to continuous and pulse electromagnetic radiation, were reported. These investigations will be discussed.

Waveform Specific Effects: What Can Epidemiological Studies Contribute?

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There exists a scientific discussion whether possible effects from electromagnetic field exposure in the radio and microwave frequency range are signal specific. In particular, it has been discussed a potential difference between sinusoidal versus non-sinusoidal waveforms. In the following will be summarized what can be concluded from epidemiological studies with respect to this open issue.

Up to now, various exposure situations have been investigated by means of epidemiological studies such as:

• different occupational exposure settings (e.g. military personnel, dielectric RF heat sealer operators, amateur radio operators, electronics technician, physiotherapists)

• different transmitters (e.g. radio: AM, FM; short-wave, LF, MW; TV)

• different phone types (cordless phones, analog mobile phones, digital mobile phones).

One might feel that a systematic evaluation of those study results will inform about waveform effect specificity. However, such an evaluation is not simple. The basic principle in epidemiologic exposure assessment is not to obtain an exact value for the total exposure for the past, but rather to divide the study collective accurately in exposed or non-exposed groups (or in groups which are exposed to a varying degree). Thus, to a certain extent every variable measured in an epidemiological study can be considered only a surrogate (or proxy) of the exposure of interest. The consequences are that the actual exposure is often rather a complex mixture of signals and frequencies than a single well-defined waveform (e.g. in occupational settings). Moreover, the exposure is physically often purely described.

Another feature of epidemiology is that in most cases only one single exposure measure has been used per study. Therefore, waveform effect specificity can only be evaluated by comparing results from different studies with the same outcome. Different results of a few available studies with the same outcome might be attributed to different electrophysical exposure characteristics; however are more likely to be caused due to differences in study design, quality, collectives, accuracy of exposure assessment, statistics, random variability, etc.

Risk of brain tumours or acoustic neuroma has been repeatedly investigated for different types of mobile phones within the same study. Thus, more truthful comparisons are possible in terms of waveform specific effects. A few studies have observed an increased risk for analog phone users but not for digital phone users. These findings are not conclusive and

may be due to methodological limitations (e.g. chance, residual confounding, exposure misclassification). If this finding would be real, it would suggest that pulsed waves are less harmful than continuous wave. However, there are additional differences between analog and digital technique which would explain dissimilar study results more likely. Analog phones have been used for a longer time period, an important aspect given the latency period of tumours. The output power of analog phones is larger than the output power of digital devices. Additionally, both techniques differs in terms of the wavelength.

In conclusion the currently available epidemiologic studies are not very informative in terms of waveform specific effects. Different results from studies of different exposure situations may be due to a multiplicity of factors. Thus, a comparison of epidemiological study results does not directly inform about waveform effect specificity. Given this constraint there is little evidence that the observed heterogeneous study results are due to a waveform specific effect.

Influence of pulse-modulated 1.8 GHz microwaves on the excitation of human nerves and muscles

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Objectives

In connection with the everyday exposure of the general population by electromagnetic fields from digital mobile communication systems different adverse effects are being reported. The potential origin of these effects is often seen not in thermic RF effects but in an athermic influence on the organism by the low frequency envelope of the pulse-modulated microwaves. The aim of this study was to examine the influence of pulse-modulated 1.8 GHz microwaves on the excitation threshold of human nerves and muscles.

Methods

Peripheral nerves and muscles of 6 volunteers were alternatively stimulated via a coaxial electrode with 1) a cathodic pulse of 1ms duration, 2) 1.8 GHz microwaves modulated by a rectangular current pulse with a frequency of 8 Hz, or 3) by a combination of both signals. The applied microwave packets have different durations up to 2 s and power up to 100 W.

In the combined stimulation the microwave packets act directly in the front of a current pulse with amplitude above the excitation threshold of individual nerves and muscles. In this way a potential conditioning of the excitation by microwave packets can be examined. The response of the stimulation was tested by means of electromyogram (EMG) and mechanogram of the appropriate muscles.

Results

The individual excitation threshold in nerves and muscles measured as the current of cathodic pulse varies in a broad range due to different composition of the tissue and distance between the coaxial electrode and the stimulated cells. The applied microwave packets alone are not able to reach the excitation thresholds of the peripheral nerves and muscles. Moreover, the conditioning of the cathodic stimulus by microwaves does not exert any influence on the EMG and mechanogram responses. In the results one cannot recognise any influence of pulse-modulated 1.8 GHz microwaves on the excitation process in nerves and muscles.

Assessment of immunotropic effects of exposure to pulse-modulated microwave radiation in relation to continuous wave exposure.

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Exposure in pulse-modulated microwave (MW) fields can influence function of the immune system, but the available data on the immunotropic potency of RF/MW radiation are still full of uncertainties and controversies.

Depending on conditions of exposure, frequency and modulation of the radiation, as well as on animal species used in the experiments, various symptoms of either stimulation or inhibition of certain immune reactions have been reported. E.g. Guy et al. (1985) in the life-time exposure of rats to MWs (pulsed 2450 MHz, SAR 0.15-0.4 W/kg) found lowered response of blood lymphocytes to mitogens (phytohaemagglutinin – PHA), while Smialowicz (1984) after exposure at the same wave frequency, although at higher power intensities (SAR 1 – 5 W/kg) reported increased mitogenic response of lymphocytes. In more recent experiments, Veyret et al. (1991) found enhancement or lowering of humoral immune response in mice exposed to 9.4 GHz at SAR 0.015 W/kg, depending on the carrier wave modulation.

In the available literature there exist no reports on complex assessment of function and responsiveness of the immune system, all investigations were aimed to evaluate selected, fragmentaric reaction of the system and/or functional response of immunocompetent cells in RF/MW-exposed subjects. Therefore, at the present state of knowledge it is not possible to conclude about the possible immunotropic potencies of RF/MW radiation, as assessment of the immunotropic potency requires a general insight into the whole complex immune network, taking into advance the immune status of the host prior to the exposure.

To determine potential immunomodulatory influences of low level microwave MW field, isolated human peripheral blood mononuclear cells (PBMC) were exposed to pulse-modulated 1300 MHz microwaves. After exposure microcultures were set up and following functional parameters of T-lymphocytes and monocytes were measured: spontaneous ^{3}HTdR incorporation, lymphocyte response to PHA and ConA, ratio of PHA and ConA response, monokine influence on lymphocyte proliferation, suppressive activity of T cells and saturation of IL-2 receptors on T lymphocytes. Concomitantly, the samples of cell-free medium removed at 24 hour from non-stimulated cultures were assessed by ELISA tests for concentration of IL-1β, IL-1ra, TNFα, IFN-γ and IL-10.

In the second set of experiments, microcultures of PBMC were set up and incubated in original miniature anechoich chamber, installed inside of the tissue culture incubator (ASSAB). Throughout the whole period of incubation (72 hrs) the microcultures were exposed to pulse-modulated 1300 MHz radiation (mean power density 10 W/m^2, SAR 0.18 W/kg). Foolowing the exposure, the cultures were terminated and functional parameters of PBMC were measured, as in pre-exposed cultures.

The results of our experiments demonstrated that both exposure of PBMC to pulse-modulated 1300 MHz microwave field at mean power density of 10 W/m^2 during cultering of cells, and pre-exposure of PBMC prior to cultering, caused measurable changes of some functional parameters of lymphocytes and monocytes, although character of these changes differs, depending on condition of the experiment.

Assessment of the immunotropic potency of RF/MW radiation has to be based on modern concepts of organization and structure of the immune system and allow for valid determination of the immune status of the exposed host. It has to be taken into advance that both stimulation and inhibition of certain immune reactions can be evoked in RF/MW-exposed subjects and that the final effect may strongly depend on the efficiency of immunity before the exposures. Therefore, it is logical to predict large individual differences (at least in human studies) in response to long-term RF/MW exposures with single subjects who may respond with considerably more pronounced (either positive or negative) shift in efficiency of the immune system that an average value for the whole group. Thus, except of analyzing mean values for the whole investigated groups, it is adviced to search for „exceptional responders" and count the frequency of such responders.

NON-THERMAL BIOLOGICAL EFEFCTS OF MICROWAVES: CURRENT KNOWLEDGE, FURTHER PERSPECTIVE AND URGENT NEEDS

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Various biological effects of non-thermal microwaves (MWs) including both adverse and beneficial effects have been described. MWs of extremely high frequency (EHF, 30-300 GHz), which are often called millimeter waves because of wavelength in vacuum, 1-10 mm, have been applied for treatment of various diseases in the former Soviet Union [1]. There is strong evidence that non-thermal biological effects of MWs on cells depend on many physical parameters and biological variables, which must be controlled in replication studies [2]. Important features of these non-thermal MWs include [2]:

- Effects of resonance type within specific frequency windows.
- Dependence on type of signal, modulation, and polarization.
- Resonance effects are observed in specific intensity windows including super-low power densities (PDs) down to 10^{-17} W/cm^2 and without evident threshold in intensity.
- With decrease in intensity, narrowing of the resonance windows and splitting of the resonances into symmetrical sub-resonances with specific efficient circular polarization occurs.
- Non-linear dependences of effects on duration of exposure and PD are observed. The MW effects are more sensitive to the duration of exposure than to the PD in the range of 10^{-17}-10^{-6} W/cm^2. Decreasing of PD by orders of magnitude can be compensated by several-fold increasing of exposure time. Therefore, the concept of dose seems to be not applicable to the effects of MWs at low intensities and duration of exposure has significantly larger role as compared to PD.
- The effects depend on cell density suggesting cell-to-cell interaction during response to MWs. Theoretical modeling of experimental data suggested that electromagnetic field is involved in this intercellular communication
- The effects depend on physiological conditions during exposure.
- Genomic differences influence response to MWs.
- Radical scavengers/antioxidants have a potential to abolish MW effects.

The basic question is how MWs at so low intensities affect living cells. Our previous studies have shown that these effects should be considered using quantum-mechanical approach [3]. This is in line with the fundamental mechanism that has been suggested by Fröhlich and predicted resonance-type interactions of MWs with living cells [4]. Our data indicated that

chromosomal DNA is the target for interaction with MWs [5, 6]. The quantum-mechanical physical model for primary reception of MWs in DNA has been proposed [7]. The physical model describing electromagnetic, mechanical and acoustic these coupled oscillations in chromosomal DNA has been developed [6].

Despite some progress, the understanding of mechanisms for non-thermal MW effects is far away from comprehensive. Beside fundamental importance, the development of comprehensive mechanisms is important because of possible adverse health effects of MWs both in working environment and residentially. The effects of MWs of mobile communications such as Global System for Mobile Communication (GSM) and Universal Global Telecommunications System (UMTS, which is used in mobile phones of the 3rd generation) are of major concern. Based on extrapolation from the EHF data, the values for half-width of resonances in the GSM/UMTS frequency range (0.9–2 GHz) were predicted to be 1-10 MHz depending on PD [8]. We have recently described the adverse effects of MWs from mobile phones on normal and transformed human lymphocytes [8, 9]. MWs from GSM and UMTS phones affected the chromatin conformation and the 53BP1/γ-H2AX proteins that produce distinct foci co-localizing with DNA double-strand breaks (DSBs) [8, 9]. Exposure at 915 MHz consistently induced statistically significant decrease in 53BP1/γ-H2AX foci in cells from normal and hypersensitive subjects. This effect was similar to the effect of heat shock. In contrast, exposure to 905 MHz induced either decrease or increase in 53BP1/γ-H2AX foci dependent on donor. The effects of GSM MWs at 905 and 915 MHz were statistically significantly different. According to our hypothesis, MWs representing wide-band signal such as UMTS may result in higher biological effects as compared to monochromatic GSM signal because of eventual “effective” frequencies within the UMTS bands [8]. The obtained data have shown that UMTS MWs (1947.4 MHz, middle channel) induce response in human lymphocytes, both from normal and hypersensitive subjects, similar to stress response induced by heat shock [10]. Remarkably, the effects of MWs from GSM/UMTS mobile phones persisted longer than after heat shock, at least up to 72 h following 1-h MW exposure.

Our data have shown that adverse effects of non-thermal MWs in the frequency range of mobile communication are dependent on carrier frequency and type of signal. Stress response and/or DNA damage are induced in human primary cells by specific MW signals at intensities well below the ICNIRP (International Committee on Non-Ionizing Radiation Protection) safety standards.

The dependence of adverse effects of non-thermal MWs from GSM/UMTS mobile phones on carrier frequency and type of signal should be further studied and taken into account in planning of *in vivo* and settings of safety standards. So far, most laboratory and epidemiological studies, including recent European REFLEX and INTERPHONE programs,

did not control important features of non-thermal MW effects and therefore, only limited conclusion can be drawn based on these studies and they cannot be compared.

The data about effects of MWs at super low intensities and significant role of duration of exposure in these effects [2, 3] along with the data showing that adverse effects of non-thermal MWs from GSM/UMTS mobile phones depend on carrier frequency and type of the MW signal [8, 10, 11] suggest that MWs from base-stations/masts can also produce adverse effects at prolonged durations of exposure and encourage the mechanistic *in vitro* studies of these effects on human primary cells using real signals from base stations/masts under well-controlled parameters of exposure.

One important conclusion stemming from the available mechanistic studies is that the epidemiological studies should not be given priority before and if proper design of these studies will be available as based on mechanistic understanding of non-thermal MW effects. This conclusion is based on three principle arguments. First, it is almost impossible to select unexposed groups because whole population in industrial countries is exposed to wide range of MW signals from various sources such as base stations/masts, WILAN, wireless phones and given that duration of exposure (around 10 years in epidemiological studies of cancer) may be more important for adverse health effects of non-thermal MWs as compared to PD [2]. Second, the adverse effects of “detrimental” signals are diluted because people are exposed to various signals/frequencies including non-effective or even hypothetically “beneficial”. At this point and before relevant understanding of mechanisms will be available, the epidemiological studies are either inconclusive, if negative, or underestimate significantly the hazard of using specific signals, if positive. Third, new signals are continuously emerging in mobile communication. Therefore, post-exposure determination of what kinds of signals were detrimental when these signals have been replaced by new detrimental signals is the real perspective to what the society will and already is faced because of prioritizing epidemiological studies by expenses of mechanistic ones as it happened in Sweden [12]. Mechanistic studies including identification of those types and frequency channels/bands for mobile communication, which do not affect human cells, and study of possibility to minimize the adverse non-thermal MW effects using different approaches, is urgently needed as the high priority task.

Financial support of Swedish Council for Working Life and Social Research, the Swedish Radiation Protection Authority, Russian Foundation for Basic Research is gratefully acknowledged.

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and genetic factors," *IEEE Transactions on Microwave Theory and Techniques*, vol. 48, pp. 2172-2179, 2000.

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Pulse modulation appears crucial for RF-EMF-induced alterations in brain physiology

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Introduction. Increasing evidence suggests that pulse-modulated, radio-frequency electromagnetic fields (RF EMF) alter brain physiology. RF EMF exposure induced reproducible changes in the nonREM sleep electroencephalogram (EEG) and altered regional cerebral blood flow (rCBF). RF EMF were also reported to influence cognitive functions. In recent studies, however, previously reported changes in cognitive functioning could not be replicated. Also the analysis of event related brain potentials during RF EMF exposure revealed conflicting results. It is possible that some of the inconsistencies are related to the spectral content of the applied RF EMF. Most studies did not investigate different spectral compositions of the emitted RF radiation. We recently found that pulse modulation of the RF EMF is necessary to induce changes in the EEG in waking and sleep.

Signal characteristics. So far, our studies were preformed with two types of pulse-modulated RF EMF: a 'handset-like' signal and a 'base-station-like' signal. The 'handset-like' signal consisted of a generic signal with a similar spectral content as the one emitted by GSM mobile phones (1 of 8 slots active). The 'base-station-like' signal consisted of a signal that mimicked the signal modulation emitted by a GSM base station (7 of 8 slots of the basic frame active). Both signals were applied at a carrier frequency of 900 MHz. It is important to note that (1) the strength and distribution of the time-averaged RF EMF absorption in the tissue were identical for both exposure signals. The spatial peak specific absorption rate (SAR) averaged over 10 g of tissue was 1W/kg for both signals. (2) Both signals had the same spectral components. (3) The 'handset-like' signal had considerably higher power in the main spectral components, i.e., at 2, 8, 217, 1736 Hz and in their harmonics. The ratio between pulse peak power and time-averaged power (crest factor) was four times higher for the 'handset-like' signal (crest factor = 4.8) compared to the 'base-station-like' signal (crest factor = 1.2). For a detailed description of the signals see Huber et al. (2005).

Summary of our findings. 1) Healthy, young subjects were exposed during an entire nighttime sleep episode to an intermittent 'base-station-like' RF EMF. Compared to a control night with sham exposure, EEG spectral power in NREM sleep was initially increased in the 10-11 Hz and 13.5-14 Hz bands (Borbély et al., 1999).

2) Healthy, young male subjects were exposed for 30 min to a 'base-station-like' RF EMF during the waking period preceding sleep. Compared to the control condition with sham

exposure, spectral power of the EEG in nonREM sleep was initially increased in the 9.75-11.25 Hz and 12.5-13.25 Hz bands (Huber et al, 2000).

3) We investigated whether pulse modulation of the signal is critical for the EEG effect. Nighttime sleep was polysomnographically recorded after 'handset-like' RF EMF exposure for 30 min during the waking period preceding sleep. 'Handset-like' RF EMF enhanced power in the alpha frequency range in the waking EEG prior to sleep onset and power in the spindle frequency range during stage 2 sleep. RF EMF without pulse modulation (continuous wave) did not enhance power in the waking or sleep EEG (Huber et al., 2002).

4) The effect of RF EMF on waking regional cerebral blood flow (rCBF) was investigated in a positron emission tomography (PET) study. Two types of RF EMF exposure were applied: a 'base-station-like' and a 'handset-like' signal. We observed an increase in relative rCBF in the dorsolateral prefrontal cortex on the side of exposure. The effect depended on the spectral power in the amplitude modulation paradigm of the RF carrier. Only 'handset-like' RF EMF exposure with stronger low frequency components and not the ‘base-station-like’ RF EMF exposure affected rCBF (Huber et al., 2002; 2005).

5) We investigated the influence of a 'handset-like' and a continuous wave RF EMF on cognitive performance during exposure and on the waking EEG after exposure. Reaction times were not affected by any field condition. 'Handset-like' EMF exposure, however, increased accuracy during exposure on the high-memory load portion of the working memory task (3-back task). EEG-analysis (eyes closed) revealed higher power in the alpha range (10.5-11 Hz) 30 min after 'handset-like' EMF exposure compared to sham control (Regel et al., in preparation).

Conclusions. Taken together, our data substantiate and corroborate the notion that pulse modulation is crucial for RF- EMF-induced alterations in brain physiology. It is important to note, however, that the changes in nonREM sleep induced by a 'base-station-like' RF EMF (Borbély et al., 1999; Huber et al., 2000) mimicked only partly, but not entirely, the changes induced by a 'handset-like' RF EMF (Huber et al., 2002). The absence of an effect of the less modulated ‘base-station-like’ signal on rCBF indicates that strong modulation components may be important to mediate a biological effect of RF EMF.

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Electropermeabilization of cells by pulses of high field strength and ultra-short duration

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Application of high-intensity electric field pulses to freely suspended cells generates a critical transmembrane voltage which leads to a drastic increase in permeability of the plasma membrane once the breakdown voltage is exceeded. It is generally accepted that membrane breakdown occurs if the induced membrane voltage reaches a value of about 1 V at room temperature. Based on this phenomenon, a wide range of practical applications of pulsed electric fields for the reversible and irreversible permeabilization of cell membranes has been identified in many areas of biotechnology and medicine. The most important biomedical application of the reversible electropermeabilization is the electroinjection technique that allows the introduction of membrane-impermeable xenomolecules (such as dyes, hormones, proteins, plasmids, etc.) into living cells. The degree of membrane electropermeabilization, molecular uptake and cell survival upon electric membrane breakdown depend critically - among other parameters - on the duration of the applied field pulses. Whereas long duration pulses of the millisecond range are generally well tolerated by bacteria, which are protected by strong cell walls, much shorter field pulses are usually required to avoid the irreversible membrane breakdown and excessive lysis of fragile eucaryotic cells, such as mammalian cells and isolated plant or yeast protoplasts. Thus, the survival of electrotransfected mammalian cells from various cell lines is substantially improved if short field pulses with the duration of 10-100 µs are applied. Use of ultra-short pulses of sub-microsecond durations further enhances survival of eucaryotic cells after electric field treatment. In the *ns*-pulse range electrodeformation forces plays the most important role in electropermeabilization. Whereas membrane charging and breakdown occur on the time scale of about 1 µs for typical mammalian cells, the transient electrodeformation force is much faster and arises in the *ns*-time range thus preceding and accompanying membrane breakdown. Therefore, the use of high-intensity DC pulses with durations shorter than the time constant of membrane charging also offers valuable insight into the biophysical mechanisms involved in electropermeabilization of cells.

Climbing the Megawatt-Per-Gram SAR Peak: The Research Into Bioeffects of Extremely High Power Microwave Pulses

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Recent advances in pulsed power technologies have resulted in increased availability and wider use of transmitters that can emit brief microwave pulses at peak powers of hundreds of megawatts and even gigawatts. High-peak, low-average power radiation from such transmitters may cause biological reactions that are qualitatively different from known microwave effects, thereby representing a new, unknown, and potentially hazardous environmental factor. However, current knowledge of bioeffects of extremely high power microwave pulses (EHPP) remains very limited. The few studies that have explored peak specific absorption rate (SAR) levels of 0.1-70 kW/g have produced isolated and generally inconclusive data [1, 2]. EHPP bioeffects at still higher peak SAR (> 100 kW/g) have not been explored until recently.

In 1998, a one-of-a-kind EHPP exposure system designed specifically for in vitro biological research was assembled and put in service at Brooks City-Base in San Antonio, TX, USA. The system operates at 9-10.5 GHz, 0.5-2 μs pulse width, up to 300 Hz pulse repetition rate; it was the first system that could produce peak SAR close to 1 MW/g in small biological samples.

By present time, EHPP effects were explored in diverse biological objects and using various endpoints, including changes in the pacemaker rate in isolated, spontaneously beating frog heart slices [3]; the growth rate of gel-suspended yeast cells [4]; function of voltage-gated calcium channels in the membrane of cultured mammalian cells [5]; synaptic transmission and long-term potentiation in isolated rat hippocampal slices [6]. In all referenced studies, EHPP exposures produced no biological effect if the temperature rise during exposure was negligible. On the contrary, when the temperature rise exceeded a threshold value (0.2-0.5 ^{o}C, depending on test sensitivity), EHPP produced same effects as CW irradiation at equal time-average SAR or conventional heating.

However, recently we have explored the effects of EHPP that were synchronized with evoked potentials of hippocampal neurons. It was found that at a certain delay between the microwave pulse and neuron firing, the EHPP exposure significantly suppressed the evoked potentials [7], and this finding has been confirmed in several replication studies. As of today, these data has provided the most compelling evidence that EHPP, under certain conditions, may produce specific bioeffects which are different from “regular” thermal effects.

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Biological effects of high-peak electric field sub-nanosecond pulses in the THz region: irradiation studies on model cell membranes

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The recent development of electromagnetic radiation sources, components and devices in the Terahertz (THz) region of the spectrum has triggered a variety of applications in the field of material science, biology and biomedicine. The THz sources employed in the different laboratories around the world very often show quite different characteristics in terms of the radiation spectral content and its temporal structure, which may affect the response of biological systems.

THz-BRIDGE, a research project funded in the Quality of Life programme of the European Union to study the interaction of THz radiation with biological systems, has recently been completed and its final report is now available. As a part of the project activity, a Compact THz Free Electron Laser (FEL) has been used at the ENEA Research Center in Frascati to perform irradiation studies on human lymphocytes and on model cell membranes in the frequency band from 90 to 150 GHz. The peculiarity of the Compact THz FEL is to generate coherent radiation in the above frequency range in the form of a "train" of micropulses of about 50 ps duration each, with 330 ps spacing between adjacent pulses. The overall duration of the train (macropulse) is 4 s. Macropulses can be produced up to a maximum repetition frequency of 10 Hz. Means are provided for adjustment and control of the peak and average power levels, as well as for frequency tuning. Although the average power of the Compact FEL is typically of the order of few mW, due to its pulsed structure, a peak power of 500 W in the macropulse and 3 kW in the micropulse can be reached at the sample surface. When the beam is focused to a spot size of about 0.5x1 cm^2 a peak electric field greater than 2 kV/cm is obtained in the micropulse.

This relatively high value of the field amplitude is capable of inducing a voltage drop across a lipid bilayer, which cannot be considered negligible when compared to the natural membrane potential. The question than arises if short THz pulses can be demodulated or “rectified” by biological systems. Interesting effects on the permeability of model membranes have been observed on Carbonic Anhydrase (CA) loaded liposomes irradiated at 130 GHz for different values of the peak electric field and modulation conditions. Any alteration of the lipid bilayer permeability induced by THz radiation was evaluated by the ability of the enzyme substrate

to diffuse across the lipid bilayer. The influx of the substrate (p-PNA) across the lipid bilayer of the liposome was followed by means of a spectrophotometric measurement of CA enzymatic activity. The highest increase of the CA activity was observed at a repetition rate of 7 Hz. Resonance effects on cationic liposomes entrapping carbonic anhydrase had already been observed in the ELF (Extremely Low Frequencies) region at 7 Hz. A significant increase of CA activity was also observed at the repetition rate of 5 and 10 Hz when the peak electric field was increased from 2.1 to 2.8 kV/cm. No significant effect was observed by irradiating the samples with 150 GHz CW THz source at the same average power level of the Compact FEL. Detailed results and a possible mechanism of interaction will be discussed.

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Screening of electromagnetic field exposures *in silico*

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Introduction. Existing and new technologies generate electromagnetic fields with many different waveforms. Biological system are orders of magnitude more complex, comprised of many cells with a huge variety of different molecules whose interactions are controlled by biological catalysts (enzymes) and by cell and organelle membrane barriers with specific transport systems (channels, transporters). However, we argue that key features of a biological system can be represented by spatially distributed biophysical mechanism models that exaggerate the coupling of a local field to a metabolically-driven biochemical process. We then argue that a necessary condition for causing a biological effect is that a field exposure must create a molecular change that exceeds changes caused by fundamental chemical noise (molecular shot noise) and other competing influences.[1]
Finally, we argue that rapid, preliminary tests of exposures can be carried out *in silico* (in a computer), through the use of increasingly realistic biological system models that estimate (1) fields at the cellular and subcellular level (microdosimetry), and (2) molecular change associated with biophysical mechanisms that couple fields to ongoing biochemical processes.

Methods. Our group has developed an initial capability for creating and solving biological system models that involve interactions with nonionizing electromagnetic fields and provide estimates of biochemical change. Digitized versions of complicated exposure waveforms can be used. 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.[2-6] The biological system models consist of a large number of interconnected local models. *In silico* (computer-based) assessments can provide rapid, approximate information for large numbers of exposures with different magnitudes and many complicated time dependencies, a capability partly analogous to high throughput screening in biotechnology.

Results. We have achieved an initial modeling/screening capability that is applicable at the tissue, 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. This *in silico* approach can provide preliminary exposure assessment for many different waveforms. 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 influences to be considered quantitatively, and a generalized, chemical-based signal-to-noise ratio, $(S/N)_{gen}$, to be used to estimate thresholds for potentially causing an effect.[1] This provides an initial basis for *in silico* screening of exposures.

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IS A SQUARE-LAW JUNCTION ESSENTIAL FOR DEMODULATION OF MODULATED WAVEFORMS IN TISSUE?

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The question of demodulation of modulated waveforms in tissue has been much discussed in connection with evaluation of putative effects of radiated waves from mobile phones on the human biosystem. It has been argued by some that demodulation "must occur in some way" and that hence, to cite the most pertinent example, the severely amplitude modulated waveform of GSM signals could be converted into low-frequency signals at 217Hz (and possibly lower frequencies). Such low frequencies will be more likely to interact in a non-thermal fashion with the functioning of the human biosystem than is currently believed possible with the carrier frequencies of the GSM system (~800 to 1900 MHz).

It is easily shown that, in a neutral medium, it is necessary to have square-law behaviour at some presumed junction carrying the induced radio frequency currents, in order to demodulate the waveform. While such square-law behaviour is well known in electronic devices, a plausible physical explanation of ways that it might be created in biological tissue has been very hard to identify: ideas that have been advanced include the use of the principle of quantum dots, but the existence of such exotic phenomena in tissue seems little less implausible than that of rectifying junctions.

On the other hand, it is much easier to envisage the existence of symmetrical voltage-limiting (saturating) regions in human tissue, such as are encountered, for instance, in metal-oxide voltage limiters. However, it is easily shown that such symmetrical junctions are not able to effect demodulation, although they will certainly generate high-order harmonics. A simple mathematically-tractable treatment of such a phenomenon can be created by presuming the device behaviour to approximate to a cube-law relationship between applied voltage and induced current. More realistic curves can be obtained by using higher-order odd powers of the voltage, but the principle is the same, and hence it is convenient to discuss the issue by using a cube law relationship as a simple exemplar:

$$i = K_a v^3(t) \qquad (1)$$

Physical consideration of the behaviour of a cube-law device suggested intuitively that, if it were biased to offset its central point from the origin of co-ordinates (zero applied voltage)

then its shape, at least under low excitation, would appear to approximate to the shape of a square-law device, and hence it might be capable of effecting demodulation (Fig. 1).

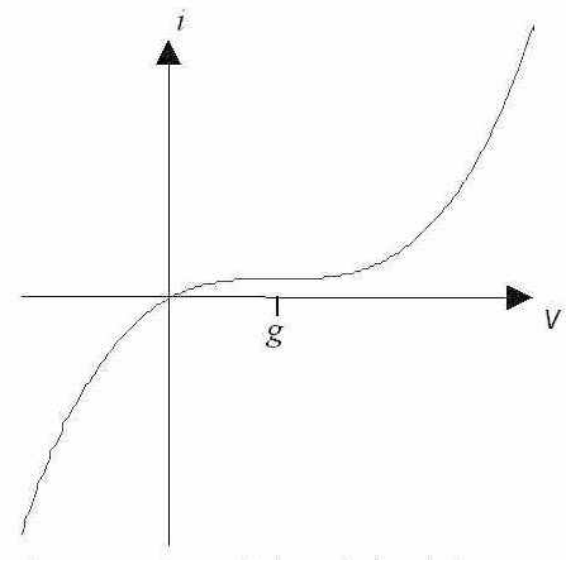

Fig. 1. Cube-law characteristic with origin offset.

It can be shown that the result of applying a modulated RF waveform to such a device is, discarding high frequency components:

$$i = K_a[-\frac{3gV_c^{\,2}}{2} - \frac{5gV_c^{\,2}}{2}xm(t) - gV_c^{\,2}x^2m^2(t)] \qquad (2)$$

where g is the offset (bias, as in Fig. 1), V_c is the carrier amplitude, x is the depth of modulation and $m(t)$ is the information signal.

This shows that the biased cube-law device can indeed cause demodulation, to an extent that increases monotonically with the amount of bias (and is zero at zero bias, as expected). This then raises the question of whether such a biased symmetrical limiting device could occur in biological tissue. As discussed above, the symmetrical limiting device appears to be physically more plausible than a square-law device and, since it is accepted that bias voltages occur at many points in the cellular structure (e.g. as implemented in the Hodgkin-Huxley approximate model [1]) this appears to give a mechanism that could indeed permit a degree of demodulation to occur, without the need for exotic mechanisms. Whether such demodulation would be significant is left for further work, as is the discussion of the probability of occurrence of the symmetrical limiting junction.

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Exposure standards for pulse-modulated fields

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ICNIRP[1] guidelines and the IEEE standard[2] for human exposure to RF fields are based on the avoidance of thermal effects of exposure. The dosimetric quantity is SAR, up to frequencies where absorption is primarily at the body's surface. SAR can be averaged over time, and as the duty factor of a pulse-modulated signal becomes smaller, at a constant power, the peak power in the pulse can become very large. The limiting factor in both these standards is the specific absorption (SA), and this is restricted in both the ICNIRP guidelines and IEEE standard. The SA restrictions are based on the avoidance of peak field effects such as the microwave auditory effect.

The ICNIRP guidelines have of course been implemented *via* the European Recommendation of public exposure to EM fields[3] although there is a subtle difference in restriction to pulsed RF fields between the Recommendation and the ICNIRP guidelines.

Some countries have set national levels, lower than the ICNIRP guidelines, for public exposures to pulse-modulated fields from telecommunications systems.

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