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PROBLEMS IN ASSESSMENT OF RISKS FROM EXPOSURES TO MICROWAVES OF MOBILE COMMUNICATION

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Since pioneering investigations published in the beginning of 1970th, various biological responses to non-thermal (NT) microwaves (MW), including adverse health effects, have been described by many research groups all over the world. There is strong evidence that the NT MW biological effects depend on several physical parameters and biological variables, which must be controlled in replication studies. Apart from the fundamental importance, the development of comprehensive mechanisms for the NT MW effects is socially important. The effects of MW of mobile communications are of major concern because of the increased exposure in many countries. It has been shown that adverse effects of NT MW from GSM/UMTS mobile phones on human lymphocytes from healthy and hypersensitive to EMF persons depend on carrier frequency and modulation. Further investigations with human primary cells, animals and volunteers are needed to elucidate possible adverse effects of MW signals that are used in wireless communication. Identification of those types and frequency channels/bands for mobile communication, which do not affect human cells, is urgently needed as the high priority task for the development of safe mobile communication. Numerous data on the NT MW effects clearly indicate that the SAR-concept alone cannot underlie the safety guidelines for chronic exposures to MW from mobile communication and other approaches are needed. However, there is not enough research information to set exposure MW standards. Various genetic and epigenetic effects of signals used in mobile communication should be studied. It has been shown that NT MW affect cells of various types including stem cells and reproductive organs. Stem cells represent especially important cellular model because recent data suggest that different cancer types, including leukemia, have a fundamentally common basis that is grounded on epigenetic changes in stem cells.

Key words: *Microwaves, health risk, non-thermal effects, chronic exposure.*

Numerous sources of mobile communication result in chronic exposure of general population to microwaves at the non-thermal levels (specific absorption rate, SAR, <2 W/kg). In the following text this exposure condition is named "NT MW" as abbreviation for non-thermal microwave exposure.

Reports on the non-thermal effects started appearing in the 1970s and have previously been reviewed [1–14]. Numerous experimental data have provided strong evidence for the NT MW effects and have also indicated dependence of these effects on several physical parameters and biological variables [15]: dependence on carrier frequency of "resonance-type" within specific frequency windows; dependence on modulation and polarization; non-linear dependence on intensity within specific intensity windows including super-low power densities (PD) down to 10^{-15} W/cm^2 that are comparable with intensities from base stations; narrowing of the frequency windows with decreasing intensity; high sensitivity of the NT MW effects to the duration and intermittence of exposure; dependence on stray electromagnetic field (EMF) of extremely low frequency (ELF); dependence on cell density that suggests cell-to-cell interaction during response to NT MW; dependence on genetic background, physiological variables during exposure and a potential of radical scavengers/antioxidants to minimize the MW effects. Most of these regularities clearly indicate that the MW effects at low intensities cannot be accounted for any type of thermal effects.

There are not yet confirmed observations that gender, individual traits, oxygen concentration, and static magnetic field during exposure may be of importance for the effects of NT MW [15].

Despite of considerable body of studies with NT MW in biology, only few studies were performed to replicate the original data on the NT MW effects. It should be noted that the "replications" are usually not comparable with the original studies because of either missing description of important parameters of exposure or significant differences in these parameters between original study and replication.

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RISK ASSESSMENT OF SIGNALS USED IN MOBILE COMMUNICATION

The safety recommendations of International Commission on Non-Ionizing Radiation Protection (ICNIRP) [16], 2 W/kg for workers and 0.8 W/kg for general population, are based on thermal effects in acute exposures and cannot protect from eventual risks of chronic exposures to the NT MW from mobile communication. Some national authorities such as Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP) have established significantly lower safety recommendations, 1 W/cm^2 for workers [17] and 10 μW/cm^2 for general population, that are based on studies with chronic exposures and acceptance of non-thermal effects [18].

It should be pointed out that before introduction of radar and microwave ovens in the 1950th and microwave links in the 1960th there was no significant microwave exposure of the population. The present generations are the first human beings being chronically exposed to NT MW from different types of mobile communication including GSM and UMTS/3G phones/base stations, WLAN (Wireless Local Area Networks), WPAN (Wireless Personal Area Networks such as Bluetooth), DECT (Digital Enhanced (former European) Cordless Telecommunications) wireless phones. The microwave links at the frequencies >6 GHz and the general broadband development in this frequency region provide rapidly increasing input to the NT MW exposure of general population.

RNCNIRP admits that the established safety standards do not correspond to the present situation when general population is exposed to variety of MW signals with durations of exposure comparable with the lifespan. Except for the inevitable exposure to MW from base stations, most part of population including children expose themselves to mobile-phone MW voluntarily [19].

So far, most of the real MW signals that are in use in mobile communication have not been tested for adverse effects. Very little research has been done with real signals and for durations and intermittences of exposure that are relevant to chronic exposures from mobile communication. In some studies, so-called "mobile communication-like" signals were investigated that in fact were different from the real exposures in such important parameters as carrier frequency, modulation, polarization, duration and intermittence. To what degree such studies are relevant to evaluation of health risks from MW of mobile communication, is not known. For example, GSM users are exposed to MW at different carrier frequencies during their talks. There are 124 different channels/frequencies, which are used in Europe for GSM900. They differ by 0.2 MHz in the frequency range from 890 MHz to 915 MHz. Mobile phone users are supplied by various frequencies from the base stations depending on number of connected users. The base station can change the frequency during the same call. It has been shown that adverse effects of NT MW from GSM mobile phones depend on carrier frequency [20, 21]. Frequency-dependent effects of GSM MW on the 53BP1/γ-H2AX DNA repair foci in human lymphocytes from healthy and hypersensitive to EMF persons, human fibroblasts and human stem cells were observed in replicated studies [20, 21].

In a Dutch study, the group of persons recruited based on their experience of being hypersensitive to MW and the healthy control group reported reduced well-being during exposure to MW of Universal Global Telecommunications System (UMTS) [22]. GSM uses GMSK modulation (Gaussian Minimum Shift Keying). Contrary to GSM phones, UMTS mobile phones of the 3rd generation (3G) use essentially QPSK (Quadrature Phase Shift Keying) modulation and irradiate wideband signals with the bandwidth of 5 MHz. UMTS MW may hypothetically result in a higher biological effect as compared to monochromatic GSM MW because of eventual "effective" frequency windows within the UMTS bands. Frequency window effects have not been studied in the UMTS frequency range. However, frequency dependences were reported for GSM900 frequency range [20] and in numerous studies using microwaves at the frequency range of 30–100 GHz [1, 7, 14, 23, 24]. Therefore, it is reasonable to expect frequency-dependent effects in the UMTS region. UMTS MW induced significant adverse effects in human lymphocytes, fibroblasts and stem cells that were more pronounced as compared to GSM effects [21].

URGENT NEEDS AND FURTHER PERSPECTIVES IN RISK ASSESSMENT

It should be anticipated that some part of population, such as children, pregnant women and groups of hypersensitive persons, may be especially sensitive to the NT MW exposures. It is becoming more and more clear that the SAR-concept that has been widely adopted for safety standards may not be useful alone for the evaluation of health risks from MW of mobile communication. How the role of other exposure parameters such as carrier frequency, modulation, polarization, duration, and intermittence of exposure should be taken into account is an urgent problem to solve. Solution of this problem would greatly benefit from the knowledge of the biophysical mechanisms of the NT MW effects. The understanding of mechanisms for the NT MW effects is currently far from being comprehensive. Many questions remain to be addressed such as whether effects of NT MW depend on static magnetic field during exposure. Besides fundamental importance, the knowledge of mechanisms for the non-thermal MW effects would facilitate the development of safe mobile communication.

So far, most laboratory and almost all epidemiological studies did not control many important features of the NT MW effects and therefore, very limited conclusion regarding health effects of MW from mobile com-

munication can be drawn from these studies. It should be noted that one group of epidemiologists with a long-lasting experience in studying relationship between mobile phone usage and cancer risk have consistently been concerned regarding importance of the type of MW signal and the exposure duration [25–28]. The group of Hardell was the first epidemiological group in attempting to study separately the MW signals from cordless phones, analogue phones and digital phones. As a rule, analogue phones had the highest association with the cancer risk. Cordless phones were associated with the risk for brain tumors, acoustic neuroma, and T-cell lymphoma stronger or in the same degree as digital and analogue phones despite significantly lower SAR values were produced by cordless phones [25, 27–29]. This important result can be considered as an independent confirmation, at the epidemiological level, of the observations from specially designed in vitro and in vivo studies that the NT MW effects depend not solely on SAR/PD, but also on other parameters. It should be added that epidemiological data are controversial and methodological differences are a subject of debates between various research groups [29, 30]. However, the approach of the Hardell's group is more valid from the mechanistic point of view and this should be taken into account when comparing with results with other epidemiological groups that are either not aware of, or ignore the complex dependencies of the NT MW effects on variety of physical and biological parameters.

The data about the effects of MW at super low intensities down to 10^{-15} W/cm^2 and significant role of duration of exposure in these effects along with the data showing that adverse effects of NT MW from GSM/UMTS mobile phones depend on carrier frequency and type of the MW signal, suggest that MW from base-stations/masts can also produce adverse effects at prolonged durations of exposure and encourage studies using real signals from base stations/masts [21].

Experimental evidence for the role of modulation in biological effects of NT MW stems from diverse experiments both in vitro and in vivo [12, 31–42]. Examples include different types of modulation such as amplitude-, speech and phase modulations. In particular, the role of modulation was examined in the group of Litovitz by studying the effects of exposure with modulated microwaves on ornithine decarboxylase (ODC) activity in L929 cells. Experiments were conducted with MW modulated in various ways, including amplitude modulation, frequency modulation, square wave modulation, and analogue and digital modulation schemes used in cellular phone communications [33]. It was found that ODC activity could be enhanced only when the amplitude of the carrier was varied periodically at extremely low frequencies. Modulation methods that did not change the amplitude of the carrier had little or no effect on ODC activity. These results corroborate the previous findings that low frequency amplitude modulation is important for the induction of biological effects by microwaves.

Significant amount of in vivo studies under varying parameters of exposure (intensity, frequency, exposure time, modulation, intermittence) have been performed in Russia/Soviet Union and published in Russian. Retrospective analysis of 52 Russian/Soviet in vivo studies with animals (mice, rats, rabbits, guinea pigs) on chronic exposure to MW has recently been published [10]. In these studies, various endpoints were measured up to 4 month of chronic exposure including analysis of: weight of animal body, histological analysis and weight of tissues, central nervous system, arterial pressure, blood and hormonal status, immune system, metabolism and enzymatic activity, reproductive system, teratogenic and genetic effects. Based on their analysis, the authors concluded that: "exposure to modulated MW resulted in bioeffects, which can be different from the bioeffects induced by continuous wave (CW) MW; exposure to modulated MW at low intensities (non-thermal levels) could result in development of unfavorable effects; direction and amplitude of the biological response to non-thermal MW, both in vitro and in vivo, depended on type of modulation; often, but not always, modulated MW resulted in more pronounced bioeffects than CW MW; the role of modulation was more pronounced at lower intensity levels". One review of the Russian/Soviet studies is available in English [43]. These authors conclude that "a number of good-quality studies have convincingly demonstrated significant bioeffects of pulsed MW. Modulation often was the factor that determined the biological response to irradiation, and reactions to pulsed and CW emissions at equal time-averaged intensities in many cases were substantially different". The findings regarding the role of modulation are extremely important to consider in NT MW exposures and should be more thoroughly studied using those specific types of modulations that are used in mobile communications.

The dependence of the NT MW effects on carrier frequency and type of signal should be taken into account when establishing safety standards and in planning of in vivo and epidemiological studies. One important conclusion stemming from the available in vitro and in vivo studies is that epidemiological studies should not be given priority for risk assessment before proper design of these studies is available based on mechanistic understanding of the NT MW effects. This conclusion is based on two principle arguments. First, it is almost impossible to select control-unexposed groups because whole population in many countries is being exposed to wide range of MW signals from various sources such as mobile phones and base stations/masts of various kinds, WLAN, WPAN, DECT wireless phones and given that duration of exposure (must be at least 10 years for cancer latency period) may be more important for the adverse health effects of NT MW than PD/SAR. It should be stressed that inappropriate defining the control-unexposed groups is a typical flaw in those epidemiological studies that are not based on mechanistic issues regarding the NT MW

effects [44]. Subjective definition of some more exposed telephone users as "exposed" and other less exposed telephone users as "unexposed controls" makes such studies inconclusive. It is clear that such epidemiological studies cannot be used as a background for risk assessment. Second, it was reported that microwaves at specific frequencies in the frequency range of 30–80 GHz can be used for treatment of various diseases [1, 6]. Moreover, bi-directional biological effects, for example either stimulation or inhibition of cell proliferation at different frequencies, were observed within this frequency range as analyzed using various biological endpoints [7, 14]. Therefore, the adverse effects of detrimental signals may be masked because people are exposed to various signals/frequencies of mobile communication, including non-effective or even hypothetically beneficial signals. Therefore, current epidemiological studies may be either inconclusive, if results are negative (no risks were found), or underestimate significantly the hazards of using specific detrimental signals, if results are positive.

The RNCNIRP proposed that guidelines and risk assessment for NT MW should be urgently developed by studies based on the next priorities: (1) Acute and chronic bioeffects of real MW signals that are currently in use (GSM, UMTS/3G phones and base stations,...) should be tested in experiments with primary human cells and using appropriate techniques. In these tests, a potential of specific MW signals to produce adverse effects should be evaluated. Those "ineffective" signals and frequency channels/bands, which do not affect human cells, should be identified for further development of safe mobile communication. (2) Studies with animals and volunteers under controlled conditions of chronic exposures to both detrimental and ineffective MW signals, as revealed by in vitro studies with primary human cells should be performed. The data obtained so far from the acute exposures of volunteers have very limited value for risk assessment because possible accumulation of effects during real chronic exposures has not been evaluated and the conditions of exposure were far away from the real situations of chronic MW exposures. (3) Development of reliable and relevant methods to control personal exposures. (4) Based on mechanistic studies, epidemiological investigations of various postponed adverse health effects should be planned. Because NT MW may affect variety of cell types, such as brain cells [45, 46], blood cells [20, 37, 47], skin and fibroblasts [21, 48–51], stem cells [21, 52, 53], reproductive organs and sperm quality [54–58], prenatal development and fertility [59, 60], different types of cancer (tumors of various localization and leukemia) and also other relevant diseases should be tested. Recent data suggest that different cancer types including leukemia have a fundamentally common basis that is grounded on epigenetic changes in stem cells [61]. Therefore, the experimental findings regarding effects of NT MW on stem cells [21, 52, 53] may be especially important for cancer risk assessment.

Interestingly enough, exposure to ELF electromagnetic fields results in similar biological effects as exposures to MW. For example, both ELF and MW exposures inhibited formation of DNA repair foci in human lymphocyte [20, 62]. ELF exposure has been reported in many epidemiological studies to be associated with the increased children leukemia. On the other hand, no association of ELF exposure with leukemia in adults was found. This discrepancy has not yet been clarified at the mechanistic basis while ELF were classified as a possible carcinogen based on these studies [63]. It is known, that stem cells are more active in children as compared to adults [64]. This may clarify the differences between results, obtained in ELF-leukemia studies with children and adults.

The epigenetic effects should also be considered in experiments with animals. Effects of NT MW should be studied in models in combination with chemicals known to produce epigenetic effects. Recent experiments have shown epigenetic effects generated by stress. Since the NT MW act as a stress factor [52, 65–67] they might produce epigenetic effects as well.

CONCLUSIONS

In conclusion, there is not enough research information to set exposure MW standards. The collaborative efforts of scientific groups within special national and international programs are needed to assess risks of the NT MW exposures. This collaboration should involve scientists with diverse expertise, including those having experience in studying the mechanisms of the NT MW effects. Otherwise, misleading conclusions or inconclusive results may be obtained.

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