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A COMPREHENSIVE REVIEW OF THE RESEARCH ON BIOLOGICAL EFFECTS OF PULSED RADIOFREQUENCY RADIATION IN RUSSIA AND THE FORMER SOVIET UNION

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INTRODUCTION

Pulsed radiofrequency (RF) radiation nowadays is among the most ubiquitous of environmental factors. Biological effects and health hazards of pulsed RF have been studied for decades, but there is still little consensus on whether the safety of pulsed RF should be given any special consideration compared to continuous wave (CW) emissions. While it is well known that pulsed fields can produce effects principally different from those of CW (e.g., an auditory effect, see Lin, 1990), potential implications of such effects for human safety and wellbeing continue to be debated.

A significant contribution to the field of bioelectromagnetics has been made by the research performed in the former Soviet Union (FSU). Unfortunately, most of this research was published in Russian; these publications are scarcely available in the West and have not ever been reviewed in English. Even some key findings, which may affect the conceptual understanding of interaction mechanisms and approaches to RF safety, seem to be not known in the West, and their replication in Western laboratories has never been attempted.

The goal of the present paper is to fill in this void and deliver a comprehensive review of the FSU research on biological effects and potential health hazards of pulsed RF radiations.

SOURCES OF INFORMATION

The principal source of information is a personal collection of scientific publications in Russian, which was accumulated as a part of a 7-year effort of one of the authors (A.G.P.) to monitor and review the Russian/FSU research in the area of electromagnetic biology. Currently, this collection includes over 1200 titles and is one of the largest of its kind.

Over 1000 of the collected studies were abstracted in English, and the abstracts are included in the electronic EMF Database (produced and distributed by Information Ventures, Inc., PA, USA). This Database (v. 3.2.4, 1999), which is the second major source of information for the current review, contains about 26000 unique citations of studies on bioeffects of electromagnetic fields (from DC to mm-waves). Out of them, there are about 3600 citations of studies performed in the FSU (and published in either Russian or English); we estimate that this bibliography includes at least 80% of related studies performed

in the FSU and published in the open (unclassified) literature since 1975 (earlier papers are only scarcely included in the Database). The EMF Database proved to be extremely convenient as a fast reference and information search engine, while the scientific quality of studies usually had to be judged from the original publications.

STATISTICS AND GENERAL NOTES

For the purpose of this review, the term "pulsed RF" applies to any pulsed, intermittent, or amplitude-modulated electromagnetic emissions with carrier frequencies from units of megahertz up to 300 GHz. A detailed search of the EMF Database revealed a total of 206 citations of pulsed RF studies performed in the FSU. For convenience, they will be referred to below as "Russian" studies, disregarding the exact place of origin (e.g., Russia or Ukraine) or the language of publication. A similar search for "non-Russian" publications on the subject revealed 1342 citations. The percentage of pulsed RF publications out of the total number in the Russian and non-Russian bibliographies was remarkably the same (6%).

These 206 citations were individually sorted to remove all meeting abstracts, review papers, and papers on dosimetry, modeling, standards setting and enforcement; then we added appropriate Russian papers not cited in the Database. The final outcome was 114 original experimental Russian studies on pulsed RF bioeffects.

Of these studies, over 70% were performed in laboratory animals. Only a few studies (<4%) employed pro- or eukaryotic cell cultures, whereas a lot of research was done in various isolated organ preparations (about 20%). A relatively large number of studies (>35%) explored effects of chronic irradiation.

It is generally accepted in Russian science that the nervous system is the most sensitive to electromagnetic radiation. Indeed, studies of pulsed RF effects on nervous system function and structure are by far the most numerous (>65%); electrophysiological and behavioral techniques are the most widely used. In a striking contrast with the Western research, not a single study has explored possible carcinogenic effects of pulsed RF; apparently, this possibility has never been a concern in Russian science.

Presumably nonthermal (or "RF-specific") bioeffects were found in 88 studies, which is more than 90% of all studies that searched for such effects. Among them, 34 studies compared bioeffects of various modulation regimens and/or those of CW versus pulsed RF. In most cases (>80%), it was found that pulsed RF effects indeed depend on modulation and/or are different from effects of CW irradiation at the equivalent time-average intensity. These data indicated that pulsing may be an important (or even the most important) factor that determines the biological effects of low-intensity RF emissions.

The most common question about Russian research in the bioelectromagnetic area is its scientific quality. Indeed, noticed flaws include unclear or invalid experiment protocols (e.g., lack of a sham-exposed control group); absence of good thermometry and dosimetry (in most animal studies, the specific absorption rate (SAR) was neither measured nor calculated); inadequate statistical analysis; failure to take into account specifics of biological experimentation with RF radiation (e.g., the use of metal recording electrodes in electrophysiological studies with RF could cause serious artifacts); and failure to report if all potential sources of the artifact were considered (e.g., the noise from a working RF transmitter can cause behavioral responses that may be misinterpreted as an RF bioeffect). While many studies were flawed in one way or another, or were poorly presented in publications, still many other Russian studies demonstrated a high-quality research.

For any study on RF bioeffects, whether flawless or not, the most critical issue is independent replication of findings. Until (or unless) proven wrong in replicative studies, the results of any reasonable-quality research deserve attention and careful consideration. That is why we attempted to address in this review all available Russian studies on pulsed RF bioeffects that meet at least the minimum scientific quality criteria. The other studies, which failed to meet these criteria (as far as it could be judged from the published material), were generally regarded as unacceptable. For example, all of the available Russian epidemiological studies with pulsed RF reported adverse health effects of exposure (such as "asthenic syndrome" or "radiofrequency disease"), but none of them showed reasonable evidence that these disorders were in fact caused by the RF exposure; besides, these studies reported too little or even no data about the exposure parameters. Because of the poor quality, none of the Russian epidemiological studies are included in the present review.

Among the "acceptable" studies, more credit was given to those that (1) reported interesting and potentially important findings, (2) presented data that were consistently reproduced over the years and were reported in more than a single publication, and (3) focused on research topics that were independently explored in different laboratories. The reviewed papers are arranged under the following categories: "*In Vitro* and *In Situ* Studies", "Animal Studies: Acute Exposure", "Animal Studies: Chronic Exposure", and "Bioeffects of Extremely High Power Pulses".

IN VITRO AND *IN SITU* STUDIES

Kim and co-authors (1986) used fluorescent probes to reveal possible effect of pulsed microwaves (800 MHz, 2 W/cm^2, 50-μs pulses at 25-100 Hz) on the state of the cell membrane in erythrocyte ghosts. The temperature of exposed samples was kept stable at 18-19 ^{o}C during 20-25 min of exposure. The experiments established that fluorescence of probes that bind to the lipid-water boundary of the membrane (2-toluidinonaphthalene-6-sulfonate, or 2,6-TNS, and 1-anilinonaphthalene-8-sulfonate, or 1,8-ANS) depended on the modulation frequency. Fluorescence of 2,6-TNS was not different from control at 25-35 Hz, but exceeded it by 12-16% at 55-65 Hz, and by 6-9% at 80-100 Hz. With 1,8-ANS, the increase in fluorescence intensity at 55 Hz was 16.9 ± 5.1%. (Hereinafter, shown average values represent the mean ± standard error, unless stated otherwise.) Fluorescence increased to the maximum after 10-20 min of exposure and then remained stable; the increase was more pronounced at higher concentrations of NaCl in the medium (up to 300 mmol). In contrast, the fluorescence parameters of piren, a hydrophobic probe, were not affected by irradiation. The authors supposed that the changes registered with fluorescent probes were induced by mechanical oscillations generated by microwave pulses.

Pashovskina and Akoev (1996) studied the effect of pulsed 2375 MHz radiation on the ATPase activity of rat actomyosin *in vitro*. Exposures for 1 min at either 40 or 200 mW/cm^2 (50- to 310-Hz modulation) heated the samples by less than 0.3 ^{o}C. ATPase activity was measured from accumulation of the inorganic phosphate (IP). Two parallel control samples, prepared together with the exposed one and from the same tissue homogenates, were used to establish the background IP contents at the time before and after the exposure. With 40 mW/cm^2 radiation, 130- and 300-Hz modulation suppressed the ATPase activity to 50 ± 3% and 9.4 ± 2.7% of the control level, respectively ($p<.05$). In contrast, 270-Hz modulation increased the ATPase activity almost 3-fold ($p<.05$). Most of other tested frequencies produced weak or moderate (< 50%) activity changes. The dependence of the effects upon the modulation frequency did not show any pattern or shape. Increasing the field intensity to 200 mW/cm^2 entirely changed the

effectiveness of the same modulation frequencies. Exposure at 130 and 300 Hz then caused ATPase activation (by 170.3 ± 3.3% and 61 ± 3.9%, respectively). The activation reached a maximum at 110-130 Hz modulation and decreased at higher and lower frequencies, forming a bell-shaped dependence. The authors concluded that ATPase activity of actomyosin showed a complex dependence upon both the field intensity and modulation, but were unable to explain this result.

Semin et al. (1995) studied the effect of weak RF on the stability of DNA secondary structure *in vitro*. DNA was exposed in the presence of glycine and formaldehyde. Aminomethynol compounds, which form in this medium, react with DNA bases at single-strand sites, which prevents recovery from damage to the DNA secondary structure. The damage accumulates during the incubation, and its amount can be estimated from the dynamics of thermal DNA denaturalization after RF or sham exposure. Samples were exposed for 30 min in an anechoic chamber at 18 ^{o}C by 10 different microwave frequencies simultaneously (4-to 8-GHz range, 25-ms pulses, 1- to 6-Hz repetition rate, 0.4 to 0.7 mW/cm^2 peak power, no heating). Parallel control samples were sham exposed in a shielded area in the same chamber. The experiments established that irradiation at 3 or 4 Hz and 0.6 mW/cm^2 peak power clearly increased the accumulated damage to the DNA secondary structure ($P<0.00001$). However, changing the pulse repetition rate to 1, 5, or 6 Hz, as well as changing the peak power to 0.4 or 0.7 mW/cm^2, eliminated the effect entirely. Thus, the effect occurred only within narrow "windows" of the peak intensities and modulation frequencies.

One more example of a "double window" was described by Gapeev et al. (1994). In this case, the effect required a certain combination of the carrier and modulation frequencies, but did not show a window dependence on the field intensity. The authors explored if the spontaneous locomotor activity of a unicellular organism *Paramecium caudatum* could be affected by irradiation with CW and modulated millimeter waves. Paramecia were placed in a thin layer of saline in a small round cuvette (7-mm diameter). Hyperpolarization of cells by a 5-fold reduction of potassium content in the saline (to 0.2 mM) made them constantly circle around in the cuvette for hours. A "motility index" (MI) was evaluated automatically by an optic probe as the amount of light reflected from cells appearing in the field of vision of a microscope during any 2-min interval. The MI increased with increasing average locomotion velocity, and decreased when cells made more turns or when the number of active cells decreased. Radiation was applied for 12 min after a 10-min stabilization period. Control samples were monitored for the same time interval, but without irradiation.

In the first set of 30 experiments, cells were exposed at 42.2 GHz (CW) at power densities from units of microwatts to tens of milliwatts per centimeter square. These exposures never affected the MI, even at the highest intensities, which caused saline heating by 1-3 ^{o}C. In the next 30 experiments, the carrier frequency was modulated at 16, 8, 1, 0.5, 0.25, 0.1, or 0.05 Hz (0.1 to 20 mW/cm^2, 0.5 duty ratio). No effect was detected, except for the combination of 0.1 Hz modulation at 0.1 mW/cm^2, which considerably decreased the MI. More accurate study of the effect of various modulation rates revealed a clear resonant dependence with a peak at 0.0956 Hz (Figure 1, A). At this modulation rate, the threshold field intensity was near 0.02 mW/cm^2. The maximum effect of about 20% MI reduction was achieved at 0.1 mW/cm^2, with no further increase at intensities of up to 50 mW/cm^2 (Figure 1, C). Further experiments demonstrated that the effect is induced only in a narrow window of carrier frequencies, with the peak at 42.25 GHz (Figure 1, B).

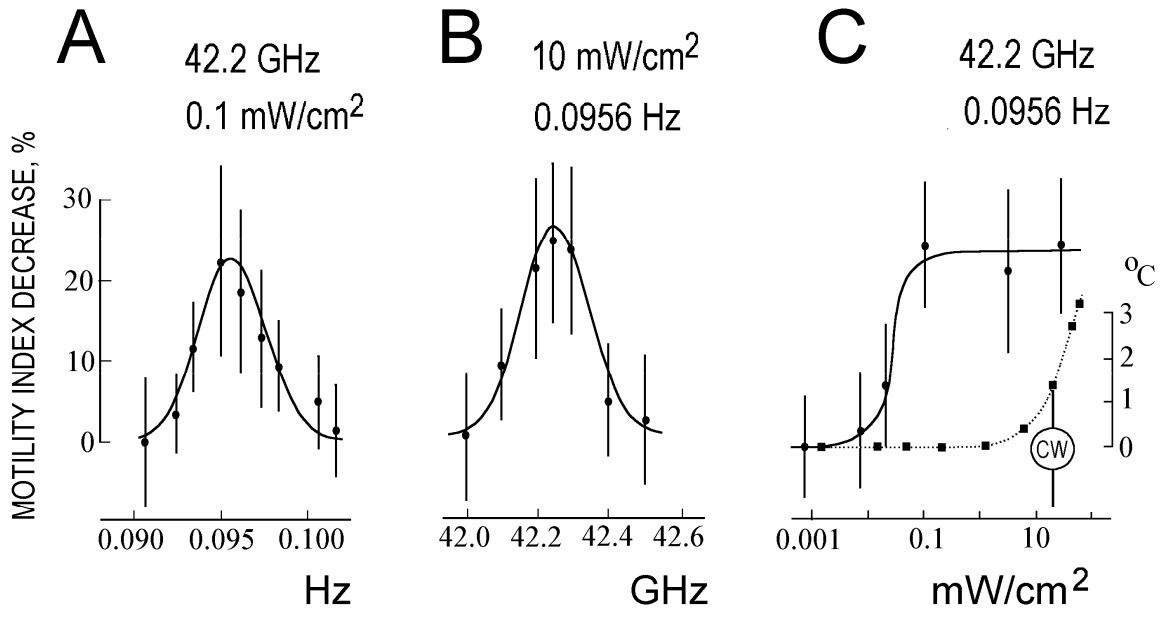

Figure 1. Effects of pulsed millimeter-wave radiation on Paramecia motility index. **A**, the effect of modulation frequency (abscissa, Hz) when the carrier frequency and power are kept constant at 42.2 GHz and 0.1 mW/cm^2. **B**, the effect of carrier frequency (abscissa, GHz) when the power and modulation are kept constant at 10 mW/cm2 and 0.0956 Hz. **C**, the effect of the incident power density (abscissa, mW/cm^2) at the resonance carrier and modulation frequencies (42.2 GHz and 0.0956 Hz). Dashed line shows the temperature increase, ^{o}C. A single datapoint ("CW") illustrates the lack of motility changes for exposure without modulation at 20 mW/cm^2. Each datapoint is the mean of 5-10 experiments; the error bars are confidence intervals at p<.05. See text for more detail. (Adopted from Gapeev et al., 1994).

This effect could not be explained by microwave heating, which reached only 0.1-0.2 ^{o}C at 5 mW/cm^2. Moreover, the effect could not be reproduced by heating with infrared radiation modulated at 0.0956 Hz. The authors suggested that the microwave-induced MI decrease could be caused by increasing the intracellular Ca^2+ level and resulting cell depolarization. However, they were unable to explain reasons for the sharp resonant dependence of the effect upon both the modulation rate and radiation frequency.

A subsequent study by the same group of authors explored the effects of CW and modulated millimeter waves on the respiratory burst in murine peritoneal neutrophils (Gapeev et al., 1997). Isolated neutrophils were exposed in the far field for 20 min in the presence of a high concentration (7.5-10 μM) of calcium ionophore A23187. After the exposure, a respiratory burst was activated by adding phorbol-12-myristate-13-acetate (1 μM), and the production of reactive oxygen species (ROS) by neutrophils was measured from luminol-dependent chemoluminescence. Experiments with CW irradiation at 50 μW/cm^2 at various fixed frequencies in the range 41.75-42.15 GHz revealed a 25% inhibition of ROS production at a "resonance" frequency of 41.95 GHz; the half width of the resonance was about 100 MHz. At 41.95 GHz, a 50% effect (half-maximum) was produced by intensities under 1 μW/cm^2. The effect reached maximum (about 24% inhibition) at 20 μW/cm^2 and remained at this plateau level at higher intensities. Modulation of 41.95-GHz radiation at 1 Hz enhanced ROS production by about 10%, modulation rates of 0.1, 16, and 50 Hz inhibited ROS production by 16-20%, and the rates of 0.5, 2, 4 and 8 Hz had no effect. In the next experiments, the modulation rate was kept constant at 1 Hz and the radiation frequency was varied. This irradiation activated ROS production in the carrier frequency band of 41.95-42.05 GHz, and suppressed it

in the band of 41.8-41.9 GHz. The authors concluded that the microwave effect on ROS production is nonthermal in nature, and is determined by specific combinations of the carrier frequency and modulation rate.

Tygranyan (1986) reported severe disturbances in isolated frog nerve and heart function if intense enough microwave pulses coincided with the "active" state of the excitable membrane (e.g., were applied during propagation of the compound action potential, CAP). In isolated frog sciatic nerve, these effects included decrease of the CAP amplitude (by 90-95%) and velocity (by 35-40%) after some 30 min of exposure. The same RF pulses delivered before, after, or asynchronously with CAP propagation produced only a subtle thermal effect. The author supposed that microwave pulse energy is converted into a mechanical pulse, which travels in a spiral between Schwann cell membranes of the nerve sheath. Due to a phase synchronism effect, the traveling pulse triggers another mechanical pulse perpendicular to the nerve surface, and the latter may be strong enough to damage the "active" nerve membrane. The author's calculations based on dielectric and mechanical properties of nerve seemed to support this hypothesis.

The findings of Tygranyan motivated Pakhomov et al. (1991) to search for similar effects in giant nerve fibers of the isolated ventral nerve cord of the earthworm *Lumbricus terrestris*. A length of about 2.5 mm of the cord was exposed in a small drop of Ringer's solution to 6.45-GHz CW or pulsed radiation, or was sham exposed. Exposure duration was from 10 to 50 min at the peak SAR from 30 to 230 mW/g. Action potentials, which were evoked by repetitive electrical stimulation and propagated along the nerve, were recorded by two pairs of electrodes, positioned immediately before and after the exposure zone. Therefore, comparison of these records provided an accurate measure indicating whether the nerve conduction in the exposure zone was affected. Microwave pulses were synchronized with the action potential crossing the exposure zone, or were delivered independently from the nerve stimulation (0.2- to 32-ms pulse width, 6- to 2000-Hz repetition rate). This study failed to produce any specific microwave effect, regardless of RF pulse parameters or their phasing with the nerve firing. However, giant nerve fibers of the earthworm ventral cord do not have a myelin sheath that was theoretically supposed to be essential for Tygranyan's effect described above. The design of the exposure cell and the carrier frequency were also different (6.45 GHz versus 800-915 MHz).

For the next study (Pakhomov et al., 1993), a microwave transmitter and irradiator were borrowed from Tygranyan's laboratory, to replicate his exposure conditions with maximum care. The experiments were performed in isolated frog sciatic nerve, which was continually stimulated at a rate of 50 twin pulses/sec for 90 min. This high-rate stimulation caused gradual decline of the nerve function, i.e., increased the CAP latency and decreased its amplitude and tracing integral. Exposures or sham exposures began 1 min after the onset of the high-rate stimulation and continued till the end of the experiment. Microwave pulses (915 MHz, 5 to 70 W/g peak SAR, 0.5- or 3-ms width) were phased with CAP in various ways, or were delivered asynchronously at a rate of 50 Hz. At the highest SAR, microwave heating could reach 2.7 ^{o}C. Regardless of phasing, SAR, or pulse width, none of the exposure regimens caused severe CAP suppression, therefore the results of Tygranyan (1986) failed to be independently confirmed.

At the same time, these experiments revealed a different microwave effect: The exposed nerves displayed a faster decrease of the CAP amplitude and tracing integral during the course of the high-rate stimulation. This effect was regarded as nonthermal or microwave-specific, since conventional heating of the superfusing solution by 3 ^{o}C during sham irradiation caused the opposite changes. Within studied limits, the magnitude of the effect showed no significant correlation with exposure parameters. In general, this microwave-induced facilitation of the nerve vitality loss was similar to the effect reported earlier by McRee and Wachtel (1980, 1982), but substantially weaker.

Two subsequent studies explored the dependence of this effect upon modulation (Pakhomov et al., 1992; Pakhomov, 1993). The course of the high-rate stimulation and exposure was reduced to 20 min. Microwave pulses of 1- to 1000-μs duration (915 MHz, 43-48 or 20-33 W/g peak SAR) were delivered at duty cycles from 1/20 to 1/4000, and were not synchronized with nerve firing. These studies identified effective and ineffective pulsing regimens. For instance, at 1/40 duty cycle and 43-48 W/g, 1- and 100-μs pulses caused a statistically significant effect, while 10- or 1000-μs pulses did not, despite the fact that the gross microwave heating by all these exposures was essentially the same.

Presumably a nonthermal effect of pulsed RF was observed in *in situ* frog heart by Grechko (1994). This wide-scale study used 1680 male frogs to compare the effects of five different types of electromagnetic fields on cardiotoxic effectiveness of a drug strophantine K. Injection of this drug caused a characteristic heart arrest in systole in about 60 min. Irradiation by 3085 MHz, 1-μs pulses at 400 Hz, 0.3-0.5 mW/cm^2 for 30 min significantly increased the latency of the heart arrest (by 17-44%). In some cases, the heart was even able to restore the activity, which never happened under sham exposure conditions. In contrast, the same irradiation for 10 min at 2-3 mW/cm^2 decreased the heart arrest latency by 10-25%.

Pakhomov et al. (1995b) attempted to replicate findings of Tinney and co-authors (1976) that microwaves can cause beating rate changes in isolated heart by stimulation of neurotransmitter release from autonomous nervous system intracardiac fiber terminals. CW exposure at 2-10 mW/g (960 MHz) was reported to cause bradycardia in isolated turtle hearts. This effect could be blocked by a parasympathetic blocker atropine, or enhanced by a sympathetic blocker propranolol. The replication experiments were performed in isolated frog heart slices, using 915 MHz radiation; exposures continued for up to 40 min at SAR levels from 0.1 to 52 mW/g (10- to 100-μs pulses at 16- to 2000-Hz repetition rates). Neither irradiation alone nor in combination with atropine or propranolol caused bradycardia in the frog heart slices. The only effect detected was a reversible beating rate increase when microwave heating exceeded 0.1 ^oC (when SAR exceeded 10 mW/g). One needs to note, however, that the studied drugs alone (i.e., without irradiation) caused marked beating rate changes in isolated turtle hearts (Tinney et al., 1976), but not in the frog heart slices, even at much higher concentrations. This finding may reflect a principal difference in physiological organization of these two heart preparations, which could be a reason for their different sensitivity to microwave radiation.

It was also reported that a caffeine antagonist, tetracaine, eliminated a nonthermal microwave effect in isolated snail neurons (Arber and Lin, 1984). Therefore, Pakhomov et al. (1995b) inferred that caffeine itself could enhance the microwave effect and tested this hypothesis in isolated frog heart slices. In contrast to atropine and propranolol, superfusion of slices with 1 mM of caffeine strongly increased the average heart power, which was calculated as a product of the beating rate and beats' amplitude. Exposure at 8-10 mW/g average SAR (1.5-ms pulses, 2.5-ms interpulse interval, 8 pulses/burst, 16 bursts/s, 915 MHz for 33 min) augmented the caffeine effect by about 15% ($p<.02$). Microwave heating was under 0.1 ^oC and could not account for this exposure effect. Moreover, the same exposure without caffeine superfusion caused no beating rate or amplitude changes.

Afrikanova and Grigoriev (1996) reported that pulsed, but not CW exposure increased the probability of heart rate changes and heart arrest in isolated and *in situ* frog heart. The effect was observed at intensities from 16 to 340 $\mu W/cm^2$ at 9.3 GHz and modulation frequencies under 100 Hz (30% modulation depth, 50% duty cycle). The maximum effect was produced by a 5-min exposure with modulation frequency changing by 1-Hz steps from 6 to 10 Hz (1 min at each step). A longer exposure with this modulation (10 or 19 min), as well as 5-min exposure using various other modulation patterns, produced weaker or different effects.

Pulsed RF effects on individual neurons in isolated brain slices were explored in studies of Zakharova and co-authors (1993, 1995, 1996). Spontaneous firing of cortical neurons was recorded by an extracellular microelectrode before, during, and after a brief (4-5 min) 900-MHz exposure at 1.4 mW/g. The reactions observed with 7-, 16-, 30-, and 60-Hz modulation (1/5 duty ratio) were a decrease of the firing rate and desynchronization of firing of individual neurons. The probability of the firing rate inhibition and its magnitude were the highest with 7- and 16-Hz modulation and the lowest with the 60-Hz modulation. For instance, 16-Hz pulses inhibited the activity in 15 out of 17 tested neurons; the firing rate could fall by 24% on the 1st minute of irradiation, and by as much as 65% on the 4th min. The rate did not recover but sometimes even decreased further after exposure. A far more intense conventional heating (by 0.33 ^{o}C/min, as opposed to 0.02 ^{o}C/min under exposure) also inhibited the activity, but just in 7 out of 13 neurons, and the firing rate did recover when the heating was over. The greater effectiveness of microwave treatment, its dependence on modulation, as well as lack of the recovery after exposure, suggested a specific microwave effect mechanism.

Philippova et al. (1988) reported an interesting effect of 900-MHz exposure on ^{3}H-camphor binding in isolated membrane fraction of rat olfactory epithelium. Under constant-temperature conditions, irradiation markedly decreased specific ^{3}H-camphor binding (down to 60-40% of the control), but did not affect its nonspecific binding. The effect depended on SAR and duration of exposure, but not on modulation in the studied range from 1 to 100 Hz. At 1 mW/g, the effect gradually increased and reached saturation after some 10-20 min of exposure. For a 15-min exposure at various SARs, the effect gradually increased with SAR and reached saturation at about 4 mW/g. The authors supposed that the observed decrease of ligand binding resulted from microwave-induced release of specific camphor-binding protein from cell membranes into solution.

The microwave effect on olfactory epithelium and neighboring respiratory epithelium was further investigated in a histological study by Popov et al. (1996). Tissue samples were obtained from Wistar rats; one sample from each animal served as a control, and the other one was exposed for 15 min at 15 W/kg to 0.9 GHz microwaves (16 Hz pulsed modulation, 50% duty ratio). Subsequent electron microscopy revealed increased vacuolization of olfactory neurons in exposed samples, which indicated dying of these cells. The most severe degenerative changes (swelling, appearance of vesicles and multilamellar structures) developed in non-myelinated axons of olfactory neurons. Concurrently, support cells displayed pronounced cytoplasmic vacuolization in apical parts of the cell body, which indicated that microwaves enhanced mucus secretion. In the respiratory epithelium, the most remarkable effect was fusion of cilia into so-called "giant cilia," which contained numerous basal bodies. These bodies formed axonemes with a typical arrangement of microtubules. Giant cilia included 5-10 or more axonemes with basal bodies and numerous vesicles (remains of fused membranes). As a rule, the cytoplasm of respiratory cells was strongly vacuolated. Overall, the authors regarded these and other observed changes as a "direct and pronounced degenerative effect of microwaves on neurons and other epithelial cells."

To complete this section on *in vitro* bioeffects, we will mention the studies that attempted to demonstrate specific bioeffects of pulsed RF, but could find either no effects, or only the effects caused by heating. Alexeev et al. (1987) could not find any but thermal effects on Ca^{2}+ transmembrane current in mollusk neurons (900 MHz, <10 min at 0.2-20 mW/g, 0.5- to 1,000-Hz modulation). Khitrov and Kakushkina (1990) observed solely thermal effects of CW or pulsed exposure on K^{+} transport and oxygen consumption in isolated rat liver tissue (2450 MHz, 0.1-5 W/g, 13-, 17-, 21-, or 25-Hz pulses at 1/1000 duty ratio). Khramov et al. (1991) could detect only thermal effects of microwaves on the electric activity of a crayfish stretch receptor (37- to 78-GHz, 10 to 250 mW/cm^{2}, from 20 sec to several hours, 0.01-1000

Hz modulation). In a study by Bolshakov and Alexeev (1992), pulsed but not CW radiation produced bursting responses of snail neurons (900 MHz, 0.5 to 15 mW/g, 0.5 to 110 Hz); however, the authors regarded this effect as possibly being an artifact from mechanical vibrations of the exposure chamber. In experiments with isolated frog heart slices, Pakhomov et al. (1995a) tested over 400 modulation regimens and concluded that changes in the beating rate and amplitude are entirely determined by the time-average SAR and microwave heating (885 or 915 MHz, 1-μs to 10-ms pulses, 1/7 to 1/100,000 duty cycle, 100 to 3000 mW/g peak SAR for 2 min).

ANIMAL STUDIES: ACUTE EXPOSURE

The possible impact of low-intensity pulsed microwaves on natural ecosystems was studied in a laboratory model using a tick *Hyalomma asiaticum* (Korotkov et al., 1996). Exposure regimens tested in this study differed in the microwave frequency, peak power, and modulation (see Table 1). Ticks were kept at a room temperature of 21-23 ^{o}C in humidified chambers. Exposures were performed at different stages of tick development (eggs, larvae, nymphs, imago); the number of specimens in each exposed group varied from 20 (experiments with larvae) to as many as 3000 (experiments with eggs). Irradiation of eggs 5-6 days after they were laid did not affect the percent of appearing larvae (95-100% in any group). At the same time, exposures significantly delayed larvae hatching. In the control group (S1), 50% of larvae appeared in 11.9±1.0 days, while in the exposed groups this interval increased to 15.3±0.1 days (R2), 25.3±0.1 days (R3), and 32.2±0.7 days (R4); R5 and R6 were not tested in these experiments. Activation of the larvae of S1- and R2-exposed groups occurred on the day of hatching, while R3 and R4 exposures delayed it by 17.0±0.4 days and 23.9±0.5 days, respectively. Exposures R4 and R5 decreased the life span of unfed larvae and nymphs by 20-30%, but this effect was not statistically significant.

Table. 1. Microwave exposure regimens* employed in the study by Korotkov et al., 1996.

Regimen	Frequency, GHz	Peak power, μW/cm^2	Modulation			
			Pulse width, ms	Pulse repetition rate, Hz	Burst duration, ms	Burst repetition rate, Hz
S1	Sham	-	-	-	-	-
R2	1-4	150	20	7	-	-
R3	3	75	**	1000	20	7
R4	3	150	**	1000	20	7
R5	1-4	750	20	2	-	-
R6	1	750	20	2	-	-

* Exposure duration in all cases was 15 min (Grigoriev, 1999).
** Pulse width for regimens R3 and R4 is not specified in the paper.

Effects of R3-R6 exposure regimens were studied in replete larvae in winter and fall tick generations. The larvae were exposed on the 10th day after feeding. The first nymphs appeared in 16-18 days after the feeding in all the groups, but their survival, molting, and life span were adversely affected by exposures.

On the whole, irradiation by pulse bursts at 3 GHz (R3 and R4) was the most effective, and the effects were more profound at the higher peak power (R4). On the contrary, the wide-band exposures (R2 and R5) were the least effective, even at 750 $\mu W/cm^2$ peak SAR. Active and fed ticks were less sensitive to microwaves than hungry specimens or those in the diapause period. The authors concluded that low intensity pulsed microwaves were a negative environmental factor for the tick *H. asiaticum*.

All other *in vivo* studies of acute bioeffects of pulsed RF were performed in warm-blooded laboratory animals. The vast majority of these studies focused on changes in the nervous system and behavior; the other ones dealt with general physiological changes (e.g., hormone production, blood composition, heart rate), and just one study explored possible genetic damage from RF irradiation (Belokhvostov et al., 1995).

In this work, male albino rats (150-200 g) were exposed in an anechoic chamber to 1-μsec, 400-Hz microwave pulses (3.085 GHz) at 5, 10, 20, or 46 mW/cm^2. The exposure lasted for 24 min or 2 hours, and the authors claimed that it caused no rise in the rectal temperature. The animals were decapitated 5 hours after the exposure, and blood taken from 6-7 rats was pooled together and considered as one sample. Blood cells were removed, and the samples were analyzed by DNA electrophoresis in polyacrylamide gel and by polymerase chain reaction (PCR). Low-molecular-weight DNA fraction (175-185 nucleotide pairs) was revealed in blood plasma in 38% of the samples from sham-exposed animals (6 samples out of 16). In exposed groups, regardless of exposure duration and intensity, this fraction was found in 80 to 100% of samples (e.g., 7 out of 8 samples after 24 min at 5 mW/cm^2, see also Figure 2, A). The DNA fraction was analyzed further by PCR to reveal complete and incomplete copies of so-called LINE elements (which are a known marker of genetic transposition in various pathologic conditions). Complete copies of the LINE element were not found in any control samples, but were present in 1 out of 7, 5 out of 7, and 1 out 7 samples after a 2-hour exposure at 5, 10, and 20 mW/cm^2, respectively (i.e., 10 mW/cm^2 was the most effective). The amount of DNA was, on the average, 2.24 times higher after 10 mW/cm^2 exposure than after 20 mW/cm^2 (n=3). Since the transposition of full copies of the LINE element is known to cause DNA rearrangements within the genome, their release into blood plasma may indicate a possible adverse effect of microwaves on genome stability.

In contrast to complete LINE elements, partial copies of the LINE sequence (with 3'-end fragment and the middle portion of the sequence) were present in all samples taken from the exposed animals. For some sequence clones, the amount of DNA was proportional to the intensity of irradiation. For example, for the clone 43 (the sequence is given in the original article), the amount of DNA increased as 1.0/1.85/1.92/2.98 in the series sham/5/10/20 mW/cm^2 (Fig. 2, B). The increased presence of the partial LINE copies does not indicate any pathological processes, but may be a useful index for biological dosimetry of microwave exposure.

Microwave exposure of the head of rabbits for 1 min at 0.2 mW/cm^2 (6 GHz, 50-Hz pulses at 1/2 duty cycle) changed the spontaneous firing rate of individual neurons in the sensomotor cortex (Lukianova et al., 1995). The firing rate was recorded extracellularly with glass microelectrodes (5- to 20- Mohm resistance). The microelectrode holder and micromanipulator were affixed to the animal's skull. These devices were custom made of plastic, to prevent any artifacts arising from metal objects introduced into the microwave field. For the same reason, plastic tubes filled with saline were used instead of metal wires to connect the microelectrode holder with an amplifier. The activity of 53 neurons was analyzed in 67 3-min experiments; each experiment was a continual activity recording for 1 min before, 1 min during, and 1 min after irradiation. The data were compared to those recorded from 54 neurons in control experiments with sham irradiation. During the exposure or sham exposure, the firing rate of an individual neuron could either increase or decrease, or showed no statistically significant changes. In the control experiments, the

firing rate decreased in 8.2% of neurons and increased in 13.07%. In the experiments with irradiation, these numbers changed to 49.5% and 6.4%, respectively ($p<.05$). Thus, the most characteristic effect of exposure was suppression of the neuron firing. This suppression developed with an average latency of 12 sec after the onset of exposure. Other parameters studied, such as spike amplitude or firing pattern, were not affected by microwaves.

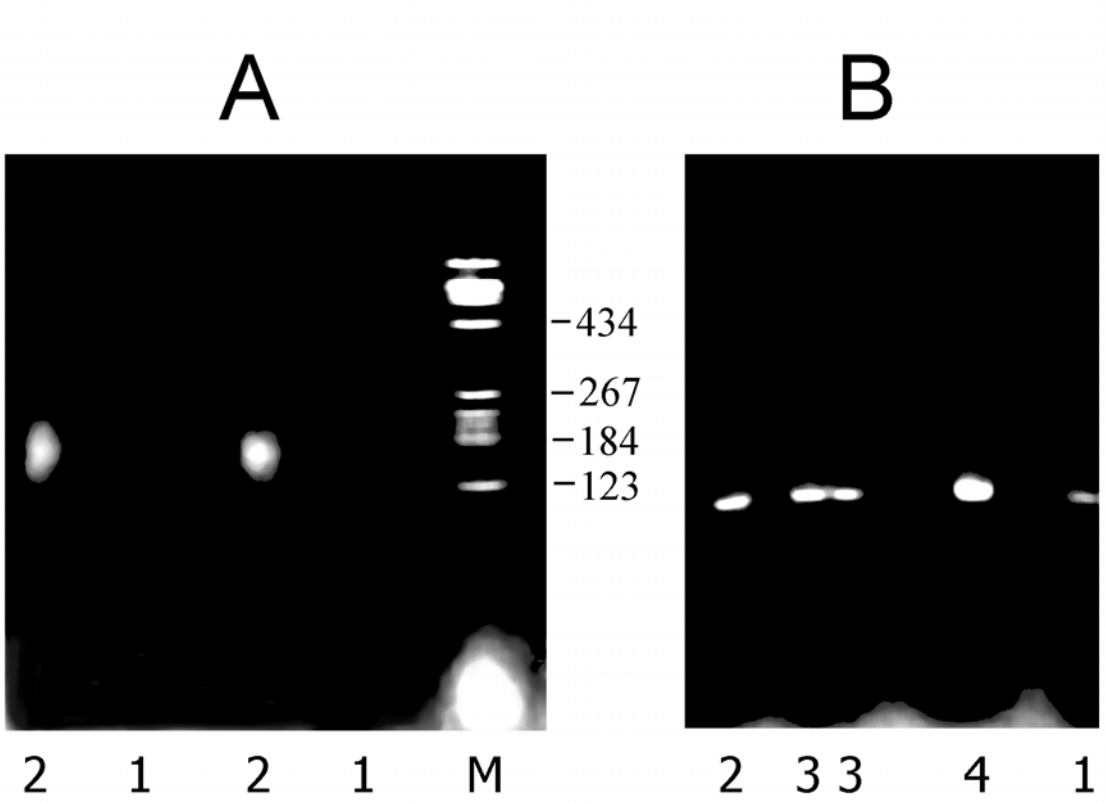

Figure 2. A, Presence of a low-weight (175-185 nucleotide pairs) DNA fraction in blood plasma of rats after pulsed RF exposure. **1:** sham exposure, **2:** 20 mW/cm^2 for 2 hours, **M:** molecular weight marker. Values to the right show the number of nucleotide pairs in marker DNA. **B**, Revealing of the 3'-end fragment of the LINE DNA element (clone 43) by 25 cycles of PCR amplification. **1:** sham exposure, **2:** 5 mW/cm^2, **3:** 10 mW/cm^2, and **4:** 20 mW/cm^2. See text for more detail. (Adopted from Belokhvostov et al., 1995).

Similar experimental techniques and protocol were employed by Moiseeva (1996) and by Lukianova and Moiseeva (1998) to study the effect of 1.5 GHz microwaves. These two papers described effects of two different pulsing regimens in an experiment with 22 rabbits. For both the regimens, the pulse width was 0.4 ms and the peak power was 0.3 mW/cm^2. These pulses were either continually delivered at a 1000-Hz repetition rate, or were arranged in 16-ms bursts (0.12 bursts/sec, 1000 pulses/sec within bursts). The data were collected from a total of 240 neurons in the sensomotor cortex and 220 neurons in the occipito-parietal cortex. Lack of statistically significant firing rate changes was the predominant response to sham exposure, while microwave irradiation markedly increased the percentage of neurons that either decreased or increased their firing rate (Table 2). Overall, about 60% of neurons reacted to microwaves. Both tested irradiation regimens caused a practically identical response. As a rule, exposure suppressed the activity in neurons with initially high firing rate, and facilitated the activity in neurons with initially low firing rate.

The magnitude of changes also was higher under microwave exposure. For exposure with repetitive microwave pulses, for example, the pre-exposure firing rate in the sensomotor cortex was 6.1 ± 0.89 pulses/sec; it increased to 11.2 ± 0.64 pulses/sec under irradiation ($p<.05$), and returned to 9.2 ± 0.58 pulses/sec after the irradiation. The respective numbers for sham exposure were 5.2 ± 1.32, 6.94 ± 1.5, and 7.8 ± 1.09 pulses/sec (the changes are not statistically significant). The average latency of the response was 10 ± 3 sec for firing activation, and 9 ± 2 sec for firing suppression.

Table 2. Changes in "spontaneous" firing rate of neurons in rabbit cerebral cortex caused by a 1-min sham or microwave exposure. (Adopted from Moiseeva, 1996, and Lukianova and Moiseeva, 1998).

Area of the cortex	Exposure regimen	Number of neurons	Type of response, % of the total number of neurons		
			Significant changes in the firing rate		Lack of changes
			Rate increase	Rate decrease	
Sensomotor	Sham	72	2.7	11.1	86.2
	Pulses[1]	105	27.6*	32.4*	40.0*
	Bursts[2]	63	24.2*	31.0*	44.8*
Occipito-parietal	Sham	73	5.5	11.0	83.5
	Pulses[1]	84	25.0*	29.8*	45.2*
	Bursts[2]	63	23.2*	30.5*	46.3*

[1] 1.5 GHz, 0.3 mW/cm^2 peak power, 0.4-ms pulses, 1000 pulses/sec.

[2] 1.5 GHz, 0.3 mW/cm^2 peak power, 0.4-ms pulses, 1000 pulses/sec within 16-ms bursts, 0.12 bursts/sec.

* The percentage of neurons is significantly different from sham control ($p<.01$, χ^2 test)

Pulsed RF effects on brain receptors have been continually studied for more than 10 years (Akoev et al., 1985, Kuznetsov et al., 1991, Kolomytkin et al., 1994, Iurinskaia et al., 1996). A brief exposure of rats to 800, 880, or 915 MHz microwaves increased radiolabelled agonist binding to glutamate receptors, decreased binding to gamma-aminobutyric acid (GABA) receptors, and decreased acetylcholinesterase activity in brain. These effects required 16-Hz modulation, at either 85% or 32% duty ratio; CW irradiation or other modulation frequencies (3 to 30 Hz) caused no statistically significant changes. Interestingly, brief (1- and 5-min) exposures often produced greater effects than prolonged exposures (15-60 min). For a 5-min exposure with 16-Hz modulation, the threshold field intensity was between 10 and 50 μW/cm^2. The magnitude of the effects gradually increased or remained almost unchanged for the field intensities from 0.1 to 1 mW/cm^2.

These findings can be illustrated in more detail by the paper of Iurinskaia et al. (1996). Four separate series of experiments were performed in male Wistar rats (150-200-g body weight). Animals were kept in normal vivarium conditions, and were made accustomed to experimental manipulations, environment, and handling for 7-10 days prior to experiments. All experiments were performed at the same time of day. The animals were exposed in groups of 3 in a plastic cage, from an open end of a waveguide. Control animals were treated in exactly the same manner and were subjected to a sham exposure. Rats were decapitated immediately after irradiation, and the brain was extracted and processed to evaluate the specific binding of radiolabelled agonists (^{3}H-glutamate and ^{3}H-muscimol) to glutamate and GABA receptors. In the first set of experiments, the authors studied the dependence of binding on the incident power density (from 0.01 to

1 mW/cm^2), when other exposure parameters were kept constant (915 MHz, 16 Hz modulation for 5 min). Microwaves increased binding of ^{3}H-glutamate and decreased binding of ^{3}H-muscimol. At 10 μW/cm^2, these indices changed to 120 ± 12% and 88 ± 12%, respectively (sham control was taken as 100%). At higher power densities, both effects gradually became more substantial (over 200% and 70-80%, respectively) and statistically significant (Figure 3, A).

The next series of experiments was focused on determining the role of modulation in the induction of these effects. Animals were exposed for 5 min at 1 mW/cm^2 (800 MHz for experiments with ^{3}H-muscimol and 915 MHz for experiments with ^{3}H-glutamate), modulated at 0, 2.5, 3, 5, 7, 16, or 30 Hz (32% duty ratio). Neither CW nor modulated regimens produced a statistically significant change in ^{3}H-muscimol binding, except for 16-Hz modulation which decreased binding to 70 ± 5%. Maximum increase in the ^{3}H-glutamate binding (to 200-220%) also occurred at 16-Hz modulation (Figure 3, B).

In the third set of experiments, the exposure duration was varied from 1 to 60 min, keeping the other parameters constant (800 or 915 MHz, 16 Hz modulation, 1 mW/cm^2). Maximum decrease in the ^{3}H-muscimol binding (to 45-50%) occurred after a 1-min exposure, and the effect gradually weakened for longer exposures. For ^{3}H-glutamate binding, the maximum effect of 200-220% was observed after a 5-min exposure; after 1-min exposure, it was 130 ± 6%. The ability to produce the effects with very low intensities of radiation, as well as dependencies on modulation and exposure duration indicated a nonthermal mechanism of the effects.

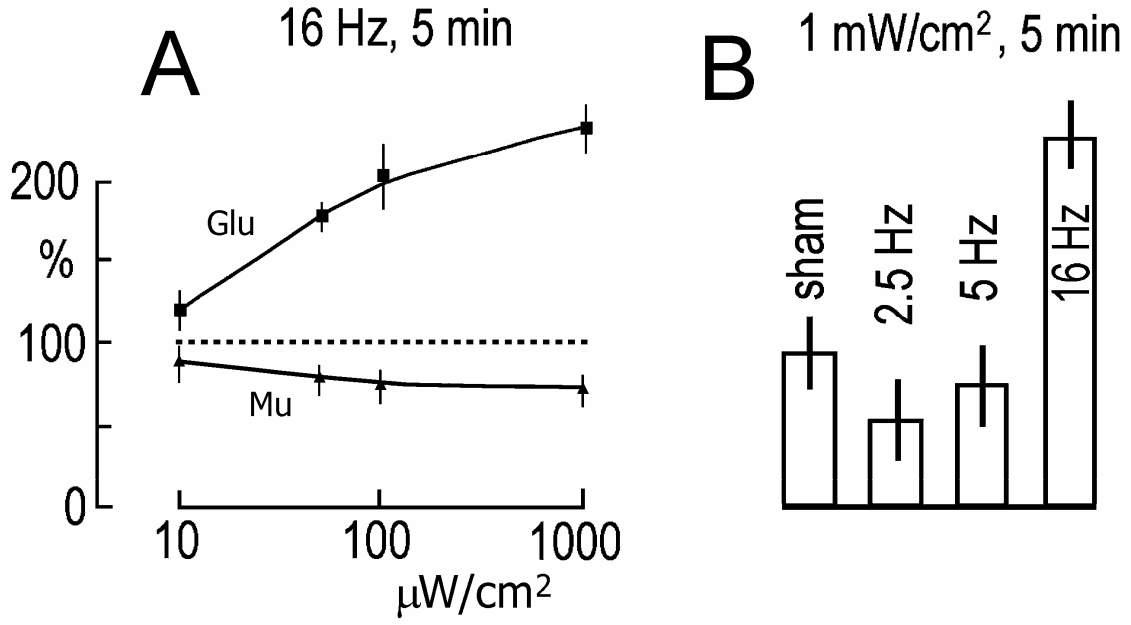

Figure 3. Changes in the binding activity of glutamate and GABA receptors in the rat brain after exposure to modulated 915-MHz microwaves. **A**, the effect of a 5-min exposure with 16-Hz modulation on binding of radiolabelled muscimol (Mu) and glutamate (Glu) at different incident power densities (abscissa, μW/cm^2). **B**, the effect of a 5-min, 1 mW/cm^2 exposure on glutamate binding at different modulation frequencies (Hz). The data shown are the mean ± s.e., in % to sham-exposed controls. See text for more detail. (Adopted from Iurinskaia et al., 1996).

In the forth set of experiments, the authors studied microwave effects on the concentration dependences of the change in binding characteristics. Irradiation only slightly affected the dissociation constant of muscimol, but decreased the number of binding sites from 17.4 ± 0.8 to 10 ± 2 pmol per mg of protein. In contrast, irradiation did not change the number of binding sites for glutamate, but decreased its dissociation constant from 277 ± 15 nM (control) to 103 ± 10 nM.

Summarizing their experimental results, the authors noted that the dynamics of the changes they observed in the state of brain receptor systems is similar to the effects produced by an electric shock, pain, or immobilization stress. They hypothesized that electromagnetic radiation works as a stressing factor, with adaptation developing under a prolonged exposure.

A series of studies performed under the leadership of K. V. Sudakov explored neurophysiological and behavioral effects of the lower RF frequencies (30 to 40 MHz, 30 to 300 V/m, 2- to 50-Hz sinusoidal modulation). The experiments were performed in rats and rabbits, and exposures lasted from 2-5 min to 45-90 min. These exposures inhibited the autonomous nervous system response to stimulation of the hypothalamus (Kashtanov and Sudakov, 1981); alleviated stress response to immobilization and electrical stimulation of the skin (Gorbunova et al., 1981); induced spreading epileptiform activity in the brain, followed by EEG suppression; induced the appearance of slow waves and even catalepsy in some animals (Sudakov and Antimonii, 1977); suppressed defensive behavior and motor activity, and inhibited extinction of the conditioned response (Sudakov, 1976, 1998). Depending on the modulation frequency, the exposure had a biphasic effect on the self-stimulatory behavior in rats (activation followed by suppression at 2-Hz modulation, or no effect followed by suppression at 7-Hz modulation), or even suppressed the self-stimulation practically from the onset of exposure at 50-Hz modulation (Antimonii et al., 1976).

However, these interesting findings should be taken with caution. One reason is that, in many cases, the authors used regular metal electrodes for brain stimulation and recording of the electric activity. The use of such electrodes during the electromagnetic field exposure could cause field distortion and various artifacts (e.g., demodulation of the field and direct stimulation of biological structures by electric current at the modulation frequency). Without independent replication in artifact-free conditions, it is not possible to judge if these findings were in fact the effect of the field, or were just a result of the flawed experiment protocol.

Konovalov and Andreeva (1989) studied microwave effects on apomorphine-induced motor stereotypy in rabbits and rats. In rabbits, a 30-min exposure of the head (880 MHz, 8 mW/cm^2, 16- or 30-Hz pulses or CW) decreased the number of "simultaneous hits" by hind limbs by 15-25%, but this difference was not statistically significant. The authors noted, however, that in 3 animals (out of 34) 16-Hz pulses decreased the number of "simultaneous hits" 3-4 times, while the other exposure regimens had only a subtle effect. In rats, a 1 mg/kg dose of apomorphine caused them to circle around the cage in the left or right direction. A single 60-min whole-body exposure with 16-Hz pulses suppressed this behavior by 21% ($p<.05$ compared with sham exposed controls); a series of 5 exposures for 60 min/day suppressed it by 40% ($p<.01$).

Grigoriev and Stepanov (1998) studied delayed effects of pulsed RF exposure on imprinting behavior in chicks. Eggs were exposed on the 16th day of incubation, for 5 min at 40 $\mu W/cm^2$ (10 GHz, 1-, 2-, 3-, 7-, 9-, or 10-Hz modulation). Two days after hatching, chicks were given a choice of two flashing light stimuli. The flashing rate of one light was the same as the modulation rate in the previous RF exposure of the egg; the flashing rate of the other light was offset by 8 Hz. It was found that chicks exposed in eggs to

9- or 10-Hz RF pulses showed preferences to the light flashes of the same frequency. Sham-exposed chicks and those exposed at other RF pulsing rates did not show a preference to either light stimulus.

A single 50-min microwave exposure at very low average intensity (15 $\mu W/cm^2$, 6 GHz, 2-Hz pulses) produced no statistically significant changes in the physiological condition of adult rabbits (Rynskov et al., 1995). The condition of microwave- and sham-exposed animals was evaluated immediately after the exposure and also on the next day. The tests employed in this study were electrocardiogram, electroencephalogram, compound myogram of *musculus gastrocnemius*, pneumogram, and blood contents of cortisol, testosterone, insulin, and thyroxin.

Lukianova and co-authors (1995) compared formation of conditioned avoidance reflexes to light, sound, pulsed microwaves (6 GHz, 50-Hz pulses, 200 $\mu W/cm^2$ average and 400 $\mu W/cm^2$ peak power), and 1000-Oe constant magnetic field. Rabbits were taught to respond to only one type of the conditioning stimuli (3 animals per group), and 4 other animals were subjected to "sham stimuli". Exposures and sham exposures were performed 6 times every other day, up to the total of 400 treatments for each animal. In 20 sec after the onset of the conditioning stimulation, the rear left extremity was stimulated with electric current, causing a flexor reaction. Withdrawal of the leg within this 20-sec interval prevented the electric stimulation and was regarded as a conditioned reflex response. Consolidation of the conditioned reflex was observed in all but one exposed animal and in none of the sham-treated controls. Consolidation took noticeably more time in the case of magnetic field exposures (243-245 combinations of stimuli) than with exposures to microwaves, sound, or light (139-154, 98-134, and 114-184 combinations, respectively). The maximum reflex percentage per 50 combinations established for the above groups was 40-60%, 30-60%, 60-78%, and 70-80%, respectively. The average latency of the reflex to the magnetic field (8.5 ± 0.12 sec) and to microwaves (7.76 ± 0.35 sec) significantly exceeded the corresponding numbers for sound (4.9 ± 0.09 sec) and light (4.47 ± 1.17 sec).

Navakatikian (1992) has described a behavioral technique sensitive enough to detect the effect of acute pulsed RF exposure at 10 $\mu W/cm^2$ (or 2.7 $\mu W/g$). The author employed a well-known shuttle-box method of studying the conditioned reflex of active avoidance, but scrupulously refined the shuttle box design and optimized the schedules of animal training and testing. Particular attention was given to selection of uniform experimental and control groups and to statistical analysis of the animals' performance data. An experiment with microwave exposure illustrated all the detail of how to use this behavioral method and how to process the raw data.

Adult male rats (280- to 360-g body weight) were trained to respond to a sound stimulus by relocating from one compartment of the shuttle box into another, in order to avoid punishment by electrical stimulation. The optimum training schedule consisted of three training series, each with 75 combinations of stimuli. One additional, so-called "testing" series (identical to the previous training series) was performed immediately after a 30-min sham or microwave exposure (3000-MHz, 10 $\mu W/cm^2$, 400-Hz pulse repetition rate, 2-μsec pulse width, 4 pulses per burst, one burst every 3.75 sec). The difference in each animal's performance in the testing series and in the last training series was taken as an individual change (IC) index. The IC values were averaged over groups of 11 exposed and 11 control rats. For the latency of the reflex response, the average IC was -0.11 ± 0.06 sec for the sham-treated group, and $+0.17 \pm 0.09$ sec in the exposed group ($p<.05$). The author noted that, for an acute exposure, the minimum microwave intensity that was reported in literature to change conditioned reflexes is 1000 $\mu W/cm^2$. The method described in this paper has therefore been proven to be sensitive enough to establish an effect of acute microwave exposure at an intensity two orders of magnitude less than previously reported.

However, the significance of this demonstration should not be overestimated. The reason is, that with the employed pulsing regimen, the incident energy density per pulse reached 9 $\mu J/cm^2$, which clearly exceeds the established threshold of 1.5-3 $\mu J/cm^2$ for auditory perception of RF pulses by rats (Chou et al., 1985). Therefore, it is not surprising that a sensitive behavioral technique could reveal some effect of a 30-min RF auditory stimulation. On the other hand, the author has reported elsewhere (Navakatikian, 1993) that the described method reliably detects the effect of 2450 MHz CW exposure at 0.1 mW/cm^2 (27 $\mu W/g$); this finding suggests that the microwave effect does not necessarily involve just auditory or thermal stimulation.

ANIMAL STUDIES: CHRONIC EXPOSURE

A substantial number of studies have explored behavioral and physiological effects of exposure conditions that imitated actual occupational or residential exposures from various military and civilian radar systems. The employed modulation schemes could be rather complex, such as regular bursts of pulses from rotating antennas or field modulation by Morse code.

Potential health effects of a coastal radar were explored by Tomashevskaia and Solenyi (1986). Field measurements established that population within 0.1-1-km distance from the coastal radar can be exposed to intermittent bursts of 400- or 800-Hz microwave pulses (3- or 10-cm wavelength) at levels from 10 to 80 $\mu W/cm^2$; the intermittence was produced by antenna rotation at 16 rpm. White mongrel rats (130 -140 g body weight) were exposed to intermittent 10-cm (2750 MHz) pulsed microwaves for 16 hours a day at 100, 500, or 2500 $\mu W/cm^2$ over a 4-month period; control animals were sham exposed. This microwave treatment significantly decreased the animals' motor activity (100 and 500 $\mu W/cm^2$), increased electrodermal sensitivity (500 and 2500 $\mu W/cm^2$), decreased the glycogen content in liver and brain (all intensities), decreased cytochrome oxidase activity in brain mitochondria (2500 $\mu W/cm^2$), and changed some immune indices (500 and 2500 $\mu W/cm^2$). Mathematical analysis of the collected data has predicted the "no-effect field intensity" to be at 10 $\mu W/cm^2$, which was therefore recommended as a maximum permissible irradiation level for residential areas.

The authors continued with studying the effects of a civil aviation radar system (Tomashevskaia and Dumanskii, 1988). Adult white rats were exposed to 400-Hz microwave pulses for 16 hours/day for 4 months using various carrier frequencies, intermittence regimens, and field intensities: (1) 2750 MHz, 50, 100, or 500 $\mu W/cm^2$, 40-μsec bursts, 1 burst per 20 sec, (2) 1310 MHz, 20 or 100 $\mu W/cm^2$, 28-μsec bursts, 1 burst per 10 sec, and (3) 850 MHz, 20, 100, or 500 $\mu W/cm^2$, 67-μsec bursts, 1 burst per 6 sec. The experiments established that exposures at 20 and 50 $\mu W/cm^2$ produced no statistically significant effects compared to sham-exposed controls. Exposures at 100 and 500 $\mu W/cm^2$ could cause statistically significant changes in the activity of several marker enzymes (cholinesterase, cytochrome oxidase, succinate dehydrogenase, and ceruloplasmin); the magnitude of changes in different tissues varied depending on the particular irradiation regimen.

Navakatikian and co-authors (1991) exposed rats to 3000-MHz pulsed radiation for 2 months, 12 hours/day during the nighttime. Bursts of 20, 4, or 2 pulses (2-μsec pulse width, 400-Hz repetition rate) were emitted every 20, 3.75, or 2.07 sec, respectively, simulating antenna rotation speeds of 3, 16, and 29 rpm. The average energy output was virtually the same for all the pulsing regimens (60, 64, and 58 pulses/min). The incident power density levels studied were 0.1, 0.5, and 2.5 mW/cm^2. Exposure effects evaluated were the animals' exploratory activity (measured as an amount of movement in a special maze)

and conditioned avoidance reflex in a shuttle box test. Most of the exposure regimens slightly stimulated the locomotor activity (except 20-pulse bursts at 0.5 and 2.5 mW/cm^2). Performance in the shuttle-box after exposures was characterized by decreased latency of responses and increased number of correct responses. Overall, the changes were interpreted as a prolonged and moderately expressed activation of the central nervous system.

Bioeffects of the above-mentioned exposure regimens were explored further and compared to the effects of 2450 MHz, 0.01-1 mW/cm^2 CW irradiation (Navakatikian and Tomashevskaya, 1994). In particular, it was found that 2-month CW exposure caused suppression of the central nervous system, in contrast to weak activation under pulsed irradiation. Histological examination of the thyroid gland revealed functional activation of the zona fasciculata after pulsed microwave exposure. Pulsed microwaves consistently and reproducibly decreased blood levels of insulin and testosterone, while CW exposure had no effect. The authors have speculated that inhibition of behavior was a direct effect of irradiation on the nervous system, whereas activation might be mediated by hormonal changes.

Another study has replicated the exposure conditions of meteorological radar personnel (Navakatikian et al., 1991). Adult female rats were subjected to simultaneous irradiation from 9375- and 1765-MHz sources for 12 hours daily, 30 min each hour. The average incident power levels for 9375 MHz were 0.12, 0.24, and 0.36 mW/cm^2; for 1765 MHz, the power output was set 24 times less, so the integral intensities used were 0.125, 0.25, and 0.375 mW/cm^2. Modulation pulse width and repetition rate were 1.1 μs, 475 Hz for 1765 MHz, and 2 μs, 300 Hz for 9375 MHz. For 9375-MHz microwaves only, the pulses were assembled into 20-msec bursts and delivered at a rate of 1 burst every 10 sec. Behavioral endpoints after 1, 2, 3, and 4 months of everyday exposure were compared with those in a sham-exposed group. The exploratory activity in animals was slightly but statistically significantly suppressed after 1-month exposure at 0.375 mW/cm^2 and after 2-months exposure at 0.125 mW/cm^2. Conditioned reflex performance in a shuttle box was suppressed after 2 months of exposure at 0.25 mW/cm^2. After 3 and 4 months of exposure, all behavioral parameters were the same as in the control group. Overall, behavioral effects observed in this study were regarded as "weak and unstable".

In a study by Grigoriev et al. (1995), adult rabbits were exposed to 1.5-GHz pulsed microwaves for 30 min a day for 1 month, excluding weekends and holidays (16-ms pulse width, 0.3 mW/cm^2 peak power, 0.12-Hz pulse repetition rate). Exposures were performed in an anechoic chamber, one animal at a time. During the exposure, animals were placed into a special Perspex cage (40 x 40 x 40 cm) with a built-in piezoelectric probe for recording motor activity. The authors performed two identical series of experiments. In each series, 5 animals were exposed and 5 were sham-exposed. Sham exposures were done in the same chamber in a random sequence with microwave exposures. In both series, the motor activity of the sham-exposed animals was maximum in the first 2 days, reflecting an orientation-exploratory reaction. The later period (until the 15th day) was characterized by extensive fluctuations of motor activity, which was interpreted as development of adaptation. After 2 weeks of treatment, motor activity stabilized at a significantly lower level, showing that adaptation is completed. In exposed animals, this decrease of motor activity was not significant, and this effect was observed in both series of experiments. For example, in the control group of the second series, the number of movements recorded during 30 min of sham exposure decreased from 117 ± 13 (the first 2 weeks' average) to 64 ± 7.8 (the second 2 weeks' average, $p<.05$). The respective numbers for microwave-exposed animals were 120 ± 11 and 105 ± 13 ($p>.05$). This irradiation effect was regarded as inhibition of the adaptive reaction, or disadaptation. The 30-min dynamics of motor activity did not show any difference between exposed and control animals, but one type of movements (rapid moving of paws up and down) significantly increased in the exposed animals in the second 2 weeks

of the experiment. This type of activity pointed to an enhancement of excitatory processes in the central nervous system, increased anxiety and distress.

Physiological effects of fields generated by ship radio transmitters (13 MHz, 250 or 500 V/m, modulated by Morse code) were reported in a series of studies by Minkina et al. (1985) and Nikitina et al. (1989a,b). Male albino rats (160-180 g body weight) were exposed to the field for 2 hours a day, 5 times a week, over a 2- or 6-week period. The authors did not supply information as to whether or not these exposures affected the body temperature of the animals. After the course of exposures, animals were decapitated and various tissues were taken for morphological and histological examination.

In the first of these studies, 2 weeks of exposure at 500 V/m slightly activated the neurosecretory function of supraoptic and paraventricular nuclei in hypothalamus. These alterations disappeared after 6 weeks of exposure, but, by this time, the mass of the adrenals was considerably decreased. Irradiation at 250 V/m for 30 days reduced the blood plasma level of corticosterone, with no other effect on adrenals or hypothalamus. Changes observed in the thyroid gland morphology indicated activation of its function by 500 V/m exposure and suppression by 250 V/m exposure. Out of studied tissues and organs, spermaries proved to be the most sensitive to irradiation. Disorders of spermatogenesis, hemorrhagia, degenerative and dystrophic changes increased with longer course and higher intensity of exposures.

The second study (Nikitina et al., 1989a) was primarily focused on cytogenetic effects of exposure (500 V/m for 10 days). Chromosome aberration frequency significantly increased in bone marrow cells (to 10-11% versus 5-6% in sham exposed controls, $p<.05$), but not in corneal cells. At the same time, the mitotic index in corneal cells fell from 1.01% to 0.66% ($p<.05$). The ascorbic acid concentration in the hypophysis and adrenal cortex increased from 264 ± 17 mg% and 403 ± 15 mg% in control animals to 361 ± 27 mg% and 478 ± 24 mg%, respectively. The size of the adrenal cortex cells decreased. In thyroid gland, the growth of colloid accumulation in follicular cavities was observed. The follicular area filled with colloid increased from $10.8 \pm 2.8\%$ to $29.7 \pm 6.1\%$ after irradiation. Irradiation disrupted spermatogenesis and reduced the mitotic activity of spermatic epithelium. The observed morphological changes indicated suppression of adrenocorticotropic hormone secretion and of the adrenal cortex and thyroid gland function. The production of luteotropic and follicle-stimulating hormones apparently was not affected.

In the third study (Nikitina et al., 1989b), the authors suggested that individual features of the animals, namely, "the type of organization of their nervous function", might play a role in their sensitivity to radiofrequency exposure. As in the previous studies, the experiments were performed in male albino rats. Based on the animals' characteristic behavior in an open-field test, they were assigned to groups with "low-entropy" (LE) and "high-entropy" (HE) organization of the nervous function. After 60 days of exposure at 500 V/m, the authors evaluated the condition of the animals by 30 various indices (morphology of thyroid, adrenals, hypophysis; blood level of testosterone, luteinizing and follicle-stimulating hormones, etc.) and the condition of their progeny on the 20th day of embryo development by 13 other indices (body mass and length, organ pathology, ossification rate, etc.). Examination of the sham-exposed group revealed 7 indices that were significantly different in the LE and HE animals; in the exposed group, there were 17 such indices. The authors provided three examples that were characteristic for these differences. The morphological changes in the thyroid gland evidenced for its activation in both LE and HE exposed animals; however, in the LE specimens this actually was manifested as an increment in the epithelial cells height, and in the HE specimens it was an increment in the cell nucleus area. Exposure significantly diminished body mass in the exposed LE animals (by about 10% compared with LE controls), but did not change it in HE animals. There was no difference in the rate of ossification in the progeny of the control HE and LE animals, while the EMF treatment decreased this index in the offsprings of the LE specimens

and increased it in the offsprings of the HE specimens. Thus, the experimental results revealed considerable differences in the EMF sensitivity between the LE and HE animals. It was recommended to consider such individual differences in future behavioral studies and in the development of safety standards.

Perhaps the most pronounced and unambiguously adverse effects of low-intensity microwave radiation were reported by Lokhmatova (1994). Effects of a 4-month exposure for 2 hours/day (3-GHz, 0.25 mW/cm^2) on reproductive organs were studied in 22 adult male rats. While the transmitter operated in a CW mode, an intermittent irradiation regimen was achieved by rotating the transmitter horn antenna at 22 rpm. A similar group of 22 animals underwent the same course of sham exposures. Morphological and histochemical analyses of the testes and epididymides were performed right after the end of the exposures and also 4 months later. The experiments revealed explicit morphofunctional disorders in RF-exposed animals. The number of normal seminiferous tubules decreased to 28.2 ± 5.3% (compared with 47.1 ± 5.3% in the controls), while the number of the tubules with dying cells increased to 27.2 ± 4.4% (14.7 ± 3.3% in the controls, $p<.05$). The number of Leydig cells markedly decreased, and some of them showed pyknotic and destructive alterations. RF exposures increased alkaline phosphatase activity in the vicinity of basal membranes and in the spermatic channel walls, and increased levels of NADH and succinate dehydrogenases. Most of these disorders showed only a subtle or no trend to recovery in 4 months after the end of exposures. The author concluded that the changes evoked by the prolonged microwave exposure are likely to result in stable impairments of production and balance of steroid hormones and premature loss of reproductive function.

BIOEFFECTS OF EXTREMELY HIGH POWER PULSES (EHPP)

Nowadays, EHPP technologies and applications are among the fastest growing areas, but very little is known about EHPP bioeffects and health hazards. The overall number of biological studies with RF pulses of 1-100 kW/g does not exceed 2-3 dozen (including meeting abstracts), and only a few isolated studies have explored still higher peak field intensities. Russian EHPP studies employed the most advanced pulsed power sources (which are still not available for biologists in the West), but the quality of reported biological research often is questionable.

Tambiev et al. (1989) studied the effect of 10-ns wide, 200 kW/cm^2 RF pulses (3-cm wavelength, 1 pulse per 6 min) on the growth rate and photosynthetic oxygen evolution in blue-green alga *Spirulina platensis* and unicellular green algae *Platymonas viridis*. It was found that exposure to 10-15 pulses stimulated cell culture growth and oxygen evolution. For example, by the 30th day after a single exposure, the biomass of *S. platensis* cultures increased by 52% in comparison with sham-exposed controls, and that of *P. viridis* increased by 17%. Maximum stimulatory effect (by up to 115%) was achieved when a treatment by 10-15 EHPP was performed immediately after a 30-min exposure to 2.2 mW/cm^2, 7.1-mm wavelength CW radiation (this mm-wave irradiation alone enhanced the growth by about 50%). The same combined treatment caused the most pronounced enhancement of the photosynthetic oxygen evolution (about 1.5 times). Further experiments demonstrated that a greater number of EHPP (20-25) had the opposite effect, i.e., suppressed the alga growth.

Deviatkov et al. (1994, 1998) studied the effects of 10-ns EHPP (3-cm wavelength, 100-MW peak output power) on malignant neoplasm development *in vivo* and *in vitro*. Exposure of Wistar rats for 9 days, 43 pulses/day, prior to inoculation with Walker carcinoma, decelerated the neoplasm growth rate 1.5 times

and increased the life expectancy by 25-30%. *In vitro* exposure of Walker carcinoma cell suspensions (80 kV/cm, 6 pulses/min for 5 to 30 min) increased the number of degenerating cells and those in a stage of lysis. Further experiments studied combined effects of EHPP and an anti-tumor drug endoksan on alveolar hepatic cancer RS-1 in rats. The drug treatment and exposures (6 pulses/min, 30 min/day for 7 days) began when the tumor volume reached 3-4 cm^3. By the 55th day after tumor inoculation, the tumor volume was 84.7 cm^3 in controls, 14 cm^3 in the endoksan-treated group, and 8.9 cm^3 in the group treated by endoksan and EHPP. A similar experiment with Lewis lung carcinoma found that EHPP treatment (6 pulses/min, 30 min/day for 4 days and then for 5 days more, after a 1-day interval) suppressed metastases, from 3.0 points (untreated controls) to 2.3 ± 0.4 (EHPP only) or 0.6 ± 0.2 (EHPP + endoksan); endoksan only decreased this index to 1.4 ± 0.4. For a health risk assessment, 58 animals were exposed to EHPP (from 130 to 720 pulses in 5 sessions) and compared with 64 control animals. Periodic examinations (3-4 times a month) over a period of 1-1.5 years have not revealed any modifications in behavioral responses or in the general state of health of the animals. Autopsy of animals in one year after the exposure did not reveal any pathological modifications in the liver, kidneys, adrenals, thymus, spleen, or other organs. We have to note, however, that lack of sufficient detail on the experimental data, protocols, dosimetry, and statistics in this study makes it difficult to evaluate the validity of reported findings.

An interesting EHPP study has been recently reported from the Institute of High Current Electronics in Tomsk, Russia (Bolshakov et al., 1999). The study was designed to check out several likely mechanisms of EHPP biological action, namely (1) membrane electroporation by high instant voltages of the electric field, (2) direct influence of the intense electric filed on macromolecular charged complexes, such as unfolded DNA sites and cytoskeleton fibers, and (3) changes in the rate of biochemical reactions, diffusion of substances and cell migration due to temperature gradients caused by EHPP absorption. These mechanisms were tested in experiments with (1) growth rate of *Escherichia coli* culture, (2) proliferation and growth of simple eukaryotic organisms (fungus *Fusarium*), and (3) ontogenetic development of *Drosophila* flies. All exposures employed a relativistic microwave generator with 200-MW output, 10-ns pulse duration, and 3-cm wavelength. The incident E-field in the exposure zone (about 25-cm diameter) was 1.5 MV/m, which corresponds to the incident power density of 300 kW/cm^2.

The growth of *E. coli* culture was measured from changes in its optical density. Two identical thermostabilized (± 1 ^oC) vials with the bacterial culture were simultaneously placed in an anechoic chamber, but one of the vials (control) was shielded from microwave radiation. Exposures for 5 or 15 min at various EHPP repetition rates (up to 100 Hz) caused no significant changes in the cell growth rate. This result was interpreted as lack of cell electroporation by the EHPP pulses.

Proliferation rate of the *Fusarium* fungus was measured by micrometry, from the diameter of cell colonies and the length of hyphae. Exposure regimens were the same as in experiments with *E. coli*; in addition, some samples were exposed in cycles (5 min exposure, 5 min pause) for a total of 1 hour at the EHPP repetition rate of 6 Hz. All tested exposure regimens substantially decelerated the growth of hyphae, on the average from 0.338 ± 0.055 mm/hour (control) to 0.242 ± 0.033 mm/hour. This deceleration was equivalent to the effect of conventional heating by 20-25 ^oC; however, heating of samples during microwave exposure was less than 1 ^oC.

For experiments with *Drosophila* eggs, larvae, and pupa, each group included at least 300 specimens. Each group was exposed or sham exposed just a single time, at different stages of ontogenesis. The exposure duration was 5 min or 60 min (12 cycles of 5-min exposure with 5-min intervals); the EHPP repetition rate was 6, 10, 16, or 22 Hz. All tested exposure parameters typically caused a 2- to 10-fold increase of cases of interrupted specimen development. Exposures of 1-hour-old embryos could cause

developmental abnormalities (morphoses) in 6 to 9% of specimens (versus zero cases in parallel controls), increased imago lethality, and caused infertility in survivors. Additional experiments with imago flies established that 5 to 12% of flies died during a 1-min exposure at EHPP repetition rates of 16, 50, and 100 Hz. At the rates of 6 and 10 Hz, no flies died, but their first generation progeny became almost entirely nonviable (34% had morphoses, 38% died on the first day, and 100% were unable to lay eggs). Since the average heating by microwave exposures was negligible, the observed effects point to certain specific mechanisms of EHPP biological action.

SUMMARY

We conclude that Russian/FSU studies constitute an important source of information on pulsed RF bioeffects. Particular emphasis in these studies was given to RF-induced changes in the nervous system function, while such issues as RF-induced carcinogenesis apparently have not been a concern and were not studied at all.

While many (perhaps, most) of the studies were flawed, a number of good-quality studies have convincingly demonstrated significant bioeffects of pulsed microwaves. 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. These results showed that bioeffects of pulsed RF may involve some specific mechanisms of interaction, which are not understood yet.

Most reported bioeffects of low-intensity pulsed microwaves were just subtle functional changes, which did not exceed the limits of normal physiological variation and could only be detected by sensitive physiological tests. However, some studies did report clearly pathogenic effects, and an independent confirmation of these findings would be of principle importance for understanding of the health hazards from RF exposure and development of safety standards. These studies deserve careful consideration and their replication in the West and/or with participation of Western scientists should be given a high priority.

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