SECTION 14

Evidence for Breast Cancer Promotion

(Melatonin Studies in Cells and Animals)

CL Sage, MA, Sage Associates,

Santa Barbara, CA USA

Prepared for the BioInitiative Working Group
July 2007

TABLE OF CONTENTS

Introduction

The subject of breast cancer and studies of melatonin has a long and rich history replete with destroyed scientific reputations and career-ending charges of misconduct of scientists who have contributed stellar scientific work that has proved extremely inconvenient for governmental agencies and military and industrial interests (Liburdy). References are given in each section below to facilitate locating the pertinent references for each section.

II. Melatonin and ELF-EMF

Evidence which supports a possible mechanism for ELF-EMF and breast cancer is the consistent finding (in five separate labs) that environmental levels of ELF-EMF can act at the cellular level to enhance breast cancer proliferation by blocking melatonin's natural oncostatic action in MCF-7 cells (Liburdy, 1993; Luben et al, 1996; Morris et al, 1998; Blackman et al, 2001; Ishido, et al, 2001). ELF-EMF levels between 0.6 and 1.2 μT have been shown to consistently block the protective effects of melatonin.

The series of papers reporting increased breast cancer cell proliferation when ELF-EMF at environmental levels negatively affects the oncostatic actions of melatonin in MCF-7 cells should warrant new public exposure guidelines or planning target limits for the public, and for various susceptible segments of the population.

References

Liburdy, R. P., T. R. Sloma, et al, 1993. ELF magnetic fields, breast cancer, and melatonin: 60 Hz fields block melatonin's oncostatic action on ER+ breast cancer cell proliferation. J of Pineal Research. 14: 89-97.

Luben et al, 1996. Replication of 12 mG EMF effects on melatonin responses of MCF-7 breast cancer cells in vitro. Abstract A-1 of the 1996 Annual review of research on biological effects of electric and magnetic fields from the generation, delivery and use of electricity, November 17-21, 1996. San Antonio, Texas, p.1

Luben et al, 1998. Independent replication of 60-Hz 1.2 μT EMF effects on melatonin and tamoxifen responses of MCF-7 cells in vitro. Abstract A-3.4, Bioelectromagnetics Society Annual Meeting, St. Pete Beach, FL. June 7-11, p 17-18.

Morris et al, 1998. In vitro exposure of MCF-7 human breast cancer cells to 60-Hz magnetic fields. Abstract p-125A, Bioelectromagnetics Society Annual Meeting, St. Pete Beach, FL. June 7-11, p 204-205.

Ishido et al, 2001. Magnetic fields (MF) of 50 Hz at 1.2 μT as well as 100 μT cause uncoupling of inhibitory pathways of adenylyl cyclase mediated by melatonin 1a receptor in MF-sensitive MCF-7 cells.

D.E. Blask, S.M. Hill, Effects of melatonin on cancer: studies on MCF-7 human breast cancer cells in culture, J. Neural Transm. Suppl. 21 (1986) 433–449.

Loberg LI et al 1999. Gene expression in human breast epithelial cells exposed to 60 Hz magnetic fields, Carcinogenesis 20 1633–1636.

III. Tamoxifen and ELF-EMF

Girgert et al (2005) reported that *"the anti-estrogenic activity of tamoxifen is reduced in two subclones of MCF-7 cells under the influence of ELF/EMF to different extent. Dose-response curves of the growth-inhibitory effect of tamoxifen are shifted towards higher concentrations leading to a reduced growth inhibition at a given concentration. Our observations confirm results from a previous report describing a reduced inhibitory effect of tamoxifen at 1^{-7} M from 40% to only 17% by exposure to an EMF of 1.2 µT"* (Harland t al, 1997). Further, Girgert et al conclude that "*From a medical point of view, it is disturbing that maximal induction of cell proliferation by tamoxifen at a field strength of 1.2 µT is observed at concentration of 10^{-6} M. This is exactly the serum concentration achieved in BC patients under standard oral therapy."* (De Cupis et al, 1997).

The Girgert et al paper confirms prior findings that environmental level ELF-EMF inhibits the antiproliferative action of tamoxifen in MCF-7 human breast cancer cells. Four other papers reporting this effect include Liburdy et al, 1997; Harland et al, 1997; Harland et al, 1999; and Blackman et al, 2001).

References

Liburdy et al, 1997. Magnetic Fields, Melatonin, Tamoxifen, and Human
Breast Cancer Cell Growth. In: Stevens R. G., Wilson B. W., Anderson L.E. (Eds). The Melatonin Hypothesis - Breast Cancer and Use of Electric Power. Battelle Press, Columbus, Richland 1997: 669- 700.

Harland et al, 1997. Environmental magnetic fields inhibit the antiproliferative action of tamoxifen and melatonin in a human breast cancer cell line. Bioelectromagnetics, 18, 555-562.

Harland et al, 1999. Evidence for a slow time-scale of interaction for magnetic fields inhibiting tamoxifen's antiproliferative action in human breast cancer cells. Cell
Biochemistry & Biophysics, 31(3), 295-306.

Blackman et al, 2001. The influence of 1.2 µT, 60 Hz magnetic fields on melatonin and tamoxifen-induced inhibition of MCF-7 cell growth. Bioelectromagnetics, 22(2), 122-128.

Girgert et al, 2005. Induction of tamoxifen resistance in breast cancer cells by ELF electromagnetic fields. Biochemical & Biophysics Research Communications, 336, 1144-1149.

A. De Cupis et al, 1997. Oestrogen/growth factor cross-talk in breast carcinoma: a specific target for novel antioestrogens, TIPS 18 245–251.

IV. Animal Studies and ELF-EMF

Anderson, L. E., G. A. Boorman, et al. (1999). Effect of 13 week magnetic field exposures on DBMA-initiated mammary gland carcinomas in female Sprague-Dawley Rats. Carcinogenesis. 20: 1615-1620.

Beniashvili, D. S., V. Bilanishvili, et al. (1991). Low-frequency electromagnetic radiation enhances the induction of rat mammary tumors by nitrosomethyl urea. Cancer Letters. 61: 75-79.

Ekstrom, T., K. H. Mild, et al. (1998). Mammary tumours in sprague-dawley rats after initiation with dmba followed by exposure to 50 Hz electromagnetic fields in a promotional scheme. Cancer Letters. 123: 107-111.

Loscher, W., M. Mevissen, et al. (1993). Tumor promotion in a breast cancer model by exposure to a weak alternating magnetic field. Cancer Letters. 71: 75-81.

Loscher, W., U. Wahnschaffe, et al. (1994). Effects of weak alternating magnetic fields on nocturnal melatonin production and mammary carcinogenesis in rats. Oncology. 51: 288-295.

Mevissen, M., A. Stamm, et al. (1993). Effects of magnetic fields on mammary tumor development induced by 7, 12-dimethylbenz(a)anthracene in rats. Bioelectromagnetics. 14: 131-143.

Mevissen M et al, 1995. In vivo exposure of rats to a weak alternating magnetic field increases ornithine decarboxylase activity in the mammary gland by a similar extent as the carcinogen DMBA, Cancer Lett. 90 (1995) 207–214.

Mevissen, M., A. Lerchl, et al. (1996). Exposure of DMBA-treated female rats in a 50 Hz, 50 microtesla magnetic field: effects on mammary tumor growth. Carcinogenesis. 17: 903-910.

Mevissen, M., A. Lerchl, et al. (1996). Study on pineal function and DMBA-induced breast cancer formation in rats during exposure to a 100-mg, 50 Hz magnetic field. J of Toxicology & Environmental Health. 48: 169-185.

Mevissen, M., M. Haussler, et al. (1998). Complex effects of long-term 50 Hz magnetic field exposure in vivo on immune functions in female Sprague-Dawley rats depend on duration of exposure. Bioelectromagnetics. 19: 259-270.

Thun-Battersby, S., M. Mevissen, et al. (1999). Exposure of Sprague-Dawley rats to a 50 Hz, 100 uTesla magnetic field for 27 weeks facillitates mammary tumorigenisis in the

V. Epidemiological Studies on Breast Cancer and ELF-EMF
Female Breast Cancer Studies

References

Milham S. (in press) 2006. Electric typewriter exposure and increased female breast cancer mortality in typists. Medical Hypotheses. Elsevier Ltd.

Cantor, K. P., M. Dosemeci, et al. (1995). Re: 'Breast cancer mortality among female electrical workers in the United States' (letter). J of the National Cancer Institute. 87: 227-228.

Cantor, K. P., P. A. Stewart, et al. (1995). Occupational exposures and female breast cancer mortality in the United States. J of Occupational & Environmental Medicine. 37: 336-348.

Demers, P. and e. al. (1991). Occupational Exposure to Electromagnetic fields and breast cancer in men. Amer J of Epidemiology. 134: 340-347.

Coogan, P. F., R. W. Clapp, et al. (1996). Occupational exposure to 60Hz Magnetic Fields and risk of breast cancer in women. Epidemiology. 7: 459-464.

Erren, T. (2001). “A meta-analysis of epidemiologic studies of electric and magnetic fields and breast cancer in women and men.” Bioelectromagnetics(Supplement 5, 2001): S105-S119.

Floderus, B., C. Stenlund, et al. (1999). Occupational magnetic field exposure and site-specific cancer incidence: a Swedish cohort study. Cancer Causes & Control. 10: 323-332.

Feychting, M., Forssen, U, L. E. Rutqvist, et al. (1998). Magnetic fields and breast cancer in Swedish adults residing near high-voltage power lines. Epidemiology.

Forssen, U. M., M. Feychting, et al. (2000). Occupational and Residential magnetic field exposure and breast cancer in females. Epidemiology. 11: 24-29.

Loomis, D. P., D. A. Savitz, et al. (1994). Breast cancer mortality among female electrical workers in the United States. J of the National Cancer Institute. 86: 921- 925.

Petralia, S. A., W.-H. Chow, et al. (1998). Occuational risk factors for breast cancer among women in Shanghai. Amer J Industrial Med. 34: 477-483.

Rosenbaum, P. F., J. E. Vena, et al. (1994). Occupational exposures associated with male breast cancer. Amer J of Epidemiology. 139: 30-36.

Stenlund, C. and B. Floderus (1997). Occupational exposure to magnetic fields in relation to male breast cancer and testicular cancer: a Swedish case-control study. Cancer Causes & Control. 8: 184-191.

Tynes, T. H., M; Andersen, A; Vistnes, AL; Haldorsen, T (1996). "Incidence of breast cancer in Norwegian female radio and telegraph operators." Cancer Causes Control 7: 197-204.

Tynes et al, 1992. Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. American Journal of Epidemiology, 136, 81-88.

Vena, J. E., J. L. Freudenheim, et al. (1994). Risk of premenopausal breast cancer and use of electric blankets. Amer J of Epidemiology. 140: 974-979.

Verkasalo et al, 1996. Magnetic fields of high voltage power lines and risk of cancer in Finnish adults: nationwide cohort study. British Medical Journal, 313(7064), 1047–1051.

VI. Male Breast Cancer Studies

References

Demers et al, 1991. Occupational exposure to electromagnetic fields and breast cancer in men. American Journal of Epidemiology, 134, 340-347.

Feychting, M., Forssen, U, L. E. Rutqvist, et al. (1998). Magnetic fields and breast cancer in Swedish adults residing near high-voltage power lines. Epidemiology.

Floderus et al, 1999. Occupational magnetic field exposure and site-specific cancer incidence: a Swedish cohort study. Cancer Causes and Control, 10, 323-332.

Floderus et al, 1994. Incidence of selected cancers in Swedish railway workers, 1961-1979. Cancer Causes and Control, 5, 189-194.

Guenel et al, 1993. Incidence of cancer in persons with occupational exposure to electromagnetic fields in Denmark. British Journal of Industrial Medicine, 50, 758-764.

Johansen et al, 1998. Risk of Cancer Among Danish Utility Workers – A Nationwide Cohort Study. American Journal of Epidemiology, 147, 548-555.

Loomis et al, 1992. Cancer of breast among men in electrical occupations. Lancet, 339, 1482-1483.

Matanowski, G. M., P. N. Breysse, et al. (1991). Electromagnetic field exposure and male breast cancer. Lancet. 337: 737.

Stendtlund et al, 1997, Occupational exposure to magnetic fields in relation to male breast cancer and testicular cancer: A Swedish case-control study. Cancer Causes & Control, 8, 184-191.

Theriault et al, 1994. . Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada and France. 1970-1989. American Journal of Epidemiology, 139, 550-572.

Tynes et al, 1994. Incidence of cancer among workers in Norwegian hydroelectric power companies. Scand. J. Work Environ. Health, 20, 339-344.

VII. Conclusions

Conclusion: The constellation of relevant scientific papers providing mutually-reinforcing evidence for an association between power-frequency electromagnetic fields (ELF-EMF) and breast cancer is strongly supported in the scientific literature.

Conclusion: ELF at environmental levels negatively affects the oncostatic effects of both melatonin and tamoxifen on human breast cancer cells. Numerous epidemiological studies over the last two decades have reported increased risk of male and female breast cancer with exposures to residential and occupational levels of ELF. Animal studies have reported increased mammary tumor size and incidence in association with ELF exposure.

Conclusion: ELF limits for public exposure should be revised to reflect increased risk of breast cancer at environmental levels possibly as low as 2 mG or 3 mG; certainly as low as 4 mG.

SECTION 15

Evidence for Disruption by Modulation Role of Physical and Biological Variables in Bioeffects of Non-Thermal Microwaves for Reproducibility, Cancer Risk and Safety Standards

2012 Supplement

Prof. Igor Belyaev, Ph D, Dr Sc

Associate Professor, Faculty of Natural Sciences

Stockholm University, Stockholm, Sweden

Head Research Scientist, Laboratory of Molecular Genetics, Cancer Research Institute

Slovak Academy of Science, Bratislava, Slovakia

Head Research Scientist, Laboratory of Radiobiology

General Physics Institute, Russian Academy of Science

Moscow, Russia

Prepared for the BioInitiative Working Group
September 2012

ABSTRACT

Diverse biological responses to non-thermal (NT) microwaves (MW), including adverse health effects related to increased cancer risk, have been studied by multiple research groups all over the world. In approximately half of these studies, no any effects were found (negative studies), while the other half reported the NT MW effects (positive studies). This fact is often referred to as non-reproducibility of the NT MW effects. In most cases, such a conclusion is based on comparing studies, which significantly differ in important biological and physical variables/parameters. The aim of this chapter is to provide an overview of the complex dependence of the NT MW effects on various physical and biological parameters, which must be controlled in replication studies. To the aim of this paper, all studies available to the author, which included analysis of different variables/parameters and reported some positive NT MW response to be a reference for analyzing its dependence on physical and biological parameters, were included. Selection criteria included relevant experimental design, methodological quality and statistical analysis. Besides dependencies on carrier frequency, modulation, genotype, physiological traits, presence of radical scavengers and antioxidants, reported by many research groups, the emerging data suggest dependencies of the NT MW effects on polarization, intermittence and coherence time of exposure, static magnetic field, electromagnetic stray fields, sex, age, individual traits, cell density during exposure. This overview provides clear evidence that in most cases, the references to non-reproducibility of the NT MW effects are not correct. Unfortunately, most reviews and panels in the field do not include analysis of various biological variables and physical parameters when comparing the data on the NT MW effects from different studies. As result, misleading conclusion is often made that MW at NT levels produce no “reproducible” effects. Our analysis suggests that different (bandwidth, frequency, modulation, polarization) NT MW signals should be considered as separate agents in setting the safety standards. The data also indicate that duration of exposure may be as important as power density (PD) and specific absorption rate (SAR), and, therefore, the "dose" and duration of exposure should also be considered in safety standards along with PD/SAR. Further evaluation of the dependencies of NT MW effects on biological and physical variables/parameters are needed for understanding the mechanisms by which NT MW affect biological systems, planning *in vivo* and epidemiological studies, setting the safety standards, and minimizing the adverse effects of MW from mobile communication.

Keywords: non-thermal effects of microwaves, mobile (cellular) phones, safety standards.

List of Abbreviations:

Anomalous viscosity time dependence (AVTD); blood-brain barrier (BBB); catalase (CAT); Digital Enhanced (former European) Cordless Telecommunications (DECT); circularly polarized (CP); continuous wave (CW); Digital Advanced Mobile Phone System (DAMPS); discontinuous transmission (DTX); electroencephalographic (EEG); electromagnetic field (EMF); embryonic stem (ES) cells; ethidium bromide (EtBr); extremely low frequency (ELF); Gaussian Minimum Shift Keying (GMSK); Ginkgo biloba (Gb); Global System for Mobile Communication (GSM); glutathione peroxidase (GSH-Px); International Commission for Non-Ionizing Radiation Protection (ICNIRP); linearly polarized (LP); malondialdehyde (MDA); micronucleus (MN) assay; microwaves (MWs); N-acetyl-beta-d-glucosaminidase (NAG); nitric oxide (NO); non-thermal (NT); ornithine decarboxylase (ODC); phorbol ester 12-myristate 13-acetate (PMA); phosphorylated H2AX histone (γ-H2AX); power density (PD); regional cerebral blood flow (rCBF); Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP); specific absorption rate (SAR); static magnetic field (SMF); superoxide dismutase (SOD); Time Division Multiple Access (TDMA); tumor suppressor p53 binding protein 1 (53BP1); ultraviolet (UV); Universal Mobile Telecommunications System (UMTS).

I. THERMAL VERSUS NON-THERMAL EFFECTS

Exposures to electromagnetic fields vary in many parameters: power (specific absorption rate, incident power density), wavelength/frequency, near field/far field, polarization (linear, circular), continues wave (CW) and pulsed fields (that include variables such as pulse repetition rate, pulse width or duty cycle, pulse shape, pulse to average power, etc.), modulation (amplitude, frequency, phase, complex), static magnetic field (SMF) and electromagnetic stray fields at the place of exposure, overall duration and intermittence of exposure (continuous, interrupted), acute and chronic exposures. With increased absorption of energy, so-called thermal effects of microwaves (MW) are usually observed that deal with MW-induced heating. Specific absorption rate (SAR) or power density (PD) is a main determinate for thermal MW effects. Several other physical parameters of exposure have been reported to be of importance for so-called non-thermal (NT) biological effects, which are induced by MW at intensities well below any measurable heating (Grundler, Jentzsch et al. 1988; Iskin 1990; Devyatkov, Golant et al. 1994; Pakhomov, Akyel et al. 1998; Adey 1999; Belyaev, Shcheglov et al. 2000; Betskii, Devyatkov et al. 2000; Banik, Bandyopadhyay et al. 2003; Grigoriev, Stepanov et al. 2003; Grigoriev 2004; Lai 2005; Belyaev 2010; Cifra, Fields et al. 2011) (Pakhomov and Murphy 2000).

Most often, current safety standards are based on thermal MW effects observed in short-term (acute) exposures. On the other hand, NT MW effects, especially those induced during prolonged (chronic) exposures, are accepted and taken into account for setting the national safety standards in some countries such as Russia (Grigoriev, Stepanov et al. 2003; Grigoriev 2004; Grigoriev, Nikitina et al. 2005). It should be noted that, in contrast to the ICNIRP (International Commission for Non-Ionizing Radiation Protection) safety standards (ICNIRP 1998) which are based on the acute thermal effects of MW, the standards adopted by the Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP) are based on experimental data from chronic (up to 4 month) exposures of animals to MW at various physical parameters including intensity, frequency and modulation, obtained from research performed in the former Soviet Union (Grigoriev, Stepanov et al. 2003; Grigoriev 2004; Grigoriev, Nikitina et al. 2005).

Since setting the current safety standards, the situation with exposure of the general population to MW has changed significantly. Nowadays, most of the human population is chronically exposed to MW signals from various sources including mobile phones and base stations. These exposures are characterized by low intensities, varieties and complexities of signals, and long-term durations of exposure that are comparable with a lifespan. So far, the “dose” (accumulated absorbed energy that is measured in radiobiology as the dose rate multiplied by exposure time) is not adopted for the MW exposures and SAR or PD is usually used for guidelines. To what degree SAR/PD can be applied to the nowadays NT MW chronic exposures is not known and the current state of research demands reevaluation of the safety standards (Grigoriev, Nikitina et al. 2005).

The literature on the NT MW effects is very broad. About half of available experimental studies report non-thermal biological effects of microwaves (Huss, Egger et al. 2007). There are four lines of evidence for the NT MW effects: (1) altered cellular responses in laboratory *in vitro* studies and results of chronic exposures *in vivo* studies (Grigoriev, Stepanov et al. 2003; Lai 2005; Cook, Saucier et al. 2006); (2) results of medical application of NT MW in the former Soviet Union countries (Sit'ko 1989; Devyatkov, Golant et al. 1994; Betskii, Devyatkov et al. 2000; Pakhomov and Murphy 2000; Pakhomov and Murphy 2000); (3) hypersensitivity to electromagnetic fields (EMF) ; (4) epidemiological studies suggesting increased cancer risks from using mobile phones longer than 10 years (Kundi, Mild et al. 2004; Lonn, Ahlbom et al. 2004; Hardell, Eriksson et al. 2005).

The first data on the NT effects of MW in so-called millimeter range (wavelength 1-10 mm in vacuum) was obtained by Vilenskaya and co-authors (Vilenskaya, Smolyanskaya et al. 1972) and Devyatkov (Devyatkov 1973). Highly resonant effects of ultra-weak MW (near 70 GHz) on the

induction of λ-phage were first established by Webb (Webb 1979), and subsequently corroborated (Lukashevsky and Belyaev 1990). In these and subsequent studies the observed spectra of MW action were found to have the following common properties: (*1*) the MW effects were strongly dependent on the frequency (frequency windows), (*2*) there was an associated power (intensity) threshold below which no effect was observed, and above which the effects of exposure depended only weakly on power over several orders of magnitude (so-called S-shaped or sigmoid dependence), (*3*) the occurrence of MW effects depended on the duration of exposure, a certain minimum duration of exposure was necessary for an effect to manifest itself. These important regularities of the NT MW effects have previously been reviewed (Postow and Swicord 1986; Grundler, Jentzsch et al. 1988; Golant 1989; Iskin 1990; Belyaev 1992; Devyatkov, Golant et al. 1994; Pakhomov, Akyel et al. 1998; Hyland 2000; Pakhomov and Murphy 2000).

The first investigations of the NT MW effects at lower frequency ranges were performed by several research groups in USSR (Presman, IuI et al. 1961; Presman 1963) and in USA by Frey (Frey 1967; Frey 1974), Blackman and colleagues (Blackman, Benane et al. 1980; Blackman, Benane et al. 1980; Joines and Blackman 1980) and Adey and colleagues (Adey, Bawin et al. 1982; Lin-Liu and Adey 1982). These groups found dependence of the NT MW effects on modulation. The effect of pulse-modulated MW was related to peak power, whereas average power was found to be relatively unimportant (Frey 1974). Frequency dependence of the MW effects have been reported (Frey 1974).

Since that time, other groups have confirmed and extended the main findings of these pioneering studies. Below, survey of recent studies, which evaluate dependence of the NT MW effects on physical parameters and biological variables, is provided.

II. FREQUENCY DEPENDENCE AND FREQUENCY WINDOWS

The effects of NT MW on DNA repair in *E. coli* K12 AB1157 were studied by the method of anomalous viscosity time dependence (AVTD) (Belyaev, Alipov et al. 1992; Belyaev, Alipov et al. 1992). The AVTD method is a sensitive technique to detect changes in conformation of nucleoids/chromatin induced by either genotoxic or stress factors (Belyaev and Harms-Ringdahl 1996; Belyaev, Shcheglov et al. 1996; Belyaev, Alipov et al. 1997; Sarimov, Malmgren et al. 2004; Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005). Significant inhibition of DNA repair was found when X-ray-irradiated cells were exposed to MW within the frequency ranges of 51.62-51.84 GHz and 41.25-41.50 GHz. The effects were observed within two “frequency windows”, both

displaying a pronounced resonance character with the resonance frequencies of 51.755 GHz and 41.32 GHz, respectively (Belyaev, Alipov et al. 1992; Belyaev, Alipov et al. 1992). Of note, these MW effects were observed at PD well below any thermal effects and could not be accounted for by heating. The frequency windows of resonance type have often been termed "resonances" as also will be used below.

The resonance frequency of 51.755 GHz was stable within the error of measurements, $\pm$1 MHz with decreasing the PD from $3 \cdot 10^{-3}$ to 10^{-19} W/cm^2 (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1996). At the same time, the half-width of the resonance decreased from 100 MHz to 3 MHz revealing an extremely sharp dependence on frequency ($Q \sim 10^4$). This sharp narrowing of the 51.755 GHz resonance with decreasing the PD from $3 \cdot 10^{-3}$ to 10^{-7} W/cm^2 followed by an emergence of new resonances, 51.675$\pm$0.001, 51.805$\pm$0.002, and 51.835$\pm$0.005 GHz (Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The half-widths of all these resonances including the main one, 51.755$\pm$0.001 GHz, were about 10 MHz at the PD of 10^{-10} W/cm^2. These data were interpreted in the framework of the model of electron-conformational interactions as a splitting of the main resonance 51.755 GHz by the MW field (Belyaev, Shcheglov et al. 1996).

The MW effects were studied at different PD and several frequencies around the resonance frequency of 51.675 GHz (Shcheglov, Belyaev et al. 1997). This resonance frequency was found to be stable, $\pm$1 MHz, within the PD range of 10^{-18} - 10^{-8} W/cm^2. Along with disappearance of the 51.675 GHz resonance response at the sub-thermal PD of 10^{-6} - 10^{-3} W/cm^2, a new resonance effect arose at 51.688$\pm$0.002 GHz (Shcheglov, Belyaev et al. 1997). This resonance frequency was also stable within the PD range studied.

Taken together, the data on NT MW effects on chromatin (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997) suggested a sharp rearrangement of the frequency spectra of MW action, which was induced by the sub-thermal MW (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The half-widths of all three resonances depended on PD, changing either from 2-3 MHz to 16-17 MHz (51.675 GHz and 51.668 GHz resonances) or from 2-3 MHz to 100 MHz (51.755 GHz resonance) (Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The data indicated also that dependencies of half-width on PD might vary for different resonance frequencies.

Significant narrowing in resonance response with decreasing PD has been found when studying the growth rate in yeast cells (Grundler 1992) and chromatin conformation in thymocytes of rats (Belyaev and Kravchenko 1994). In the Gründler's study, the half-width of the resonance (near 41 GHz) decreased from 16 MHz to 4 MHz as PD decreased from 10^{-2} W/cm^2 to 5 pW/cm^2 (Grundler 1992).

Thus, the results of studies with different cell types indicate that narrowing of the resonance window upon decrease in PD is one of the general regularities in cell response to NT MW. This regularity suggests that many coupled oscillators are involved non-linearly in the response of living cells to NT MW as has previously been predicted by Fröhlich (Frohlich 1968).

Gapeev et al. studied effects of MW exposure (frequency range 41.75-42.1 GHz, frequency increment 50 MHz, PD 240 $\mu W/cm^2$) on the respiratory burst induced by calcium ionophore A23187 and phorbol ester 12-myristate 13-acetate (PMA) in the peritoneal neutrophils of mice (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). MW inhibited the respiratory burst. MW effect displayed resonance-like dependence on frequency, the resonance frequency and half-width of the resonance being 41.95 GHz and 160 MHz, respectively (Q= 260) (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). In other studies, Gapeev et al. analyzed acute zymosan-induced paw edema in mice (Gapeyev, Mikhailik et al. 2008; Gapeyev, Mikhailik et al. 2009). MW exposure of animals at the PD of 0.1 mW/cm^2 resulted in decrease of the paw edema that was frequency-dependent in the range of 42-43 GHz.

Based on the extrapolation from the data obtained in the extremely high frequency range (30-300 GHz), the values for half-width of resonances at the frequency range of mobile phones (0.9–2 GHz) were estimated to be 1-10 MHz (Sarimov, Malmgren et al. 2004). Effects of GSM (Global System for Mobile Communication) MW on chromatin conformation and 53BP1 (tumor suppressor p53 binding protein 1)/γ-H2AX (phosphorylated H2AX histone) DNA repair foci in human lymphocytes were studied in this frequency range (Sarimov, Malmgren et al. 2004; Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). These MW effects depended on carrier frequency (Sarimov, Malmgren et al. 2004; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). This dependence was replicated in independent experiments with lymphocytes from twenty six healthy and hypersensitive persons (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009).

Tkalec and colleagues exposed duckweed (*Lemna minor L.*) to MW at the frequencies of 400, 900, and 1900 MHz (Tkalec, Malaric et al. 2005). The growth of plants exposed for 2 h to a 23 V/m electric field of 900 MHz significantly decreased in comparison with the control, while an electric field of the same strength but at 400 MHz did not have such effect. A modulated field at 900 MHz strongly inhibited the growth, while at 400 MHz modulation did not influence the growth significantly. At both frequencies, a longer exposure mostly decreased the growth and the highest electric field (390 V/m) strongly inhibited the growth. Exposure of plants to lower field strength (10 V/m) for 14 h caused a significant decrease at 400 and 1900 MHz while 900 MHz did not influence the growth. Peroxidase activity in exposed plants varied, depending on the exposure characteristics.

Observed changes were mostly small, except in plants exposed for 2 h to 41 V/m at 900 MHz where a significant increase (41%) was found. The authors concluded that MW might influence plant growth and, to some extent, peroxidase activity. However, the effects of MW strongly depended on the characteristics of the field exposure such as frequency and modulation. These dependences were replicated in further studies (Tkalec, Malaric et al. 2007; Tkalec, Malaric et al. 2009).

Remondini et al. analyzed changes in gene expression in human EA.hy926 endothelial cells using gene microarrays (Remondini, Nylund et al. 2006). Cells were exposed to MW (SAR 1.8-2.5 W/kg, 1 h exposure) either at 900-MHz GSM Basic mode or 1800-MHz GSM Basic mode. Exposure to 900 MHz resulted in up-regulation in 22 genes and down-regulation in 10 genes. No significant change in gene expression was observed after exposure to 1800 MHz.

III. NON-LINEARITY: SIGMOID INTENSITY DEPENDENCES AND POWER WINDOWS

Devyatkov with colleagues have found and published in Russian that wide variety of NT MW effects *in vitro* and *in vivo* display sigmoid dependence on intensity above certain intensity thresholds (Devyatkov 1973).

In English literature, one of the earliest observation of threshold in response to NT MW was published by Frey (Frey 1967). In this study, the threshold of 30 μW/cm2 was found in the study by Frey on Brain stem evoked responses to RF in cats (Frey 1967). This value was 4 orders of magnitude lower then intensities needed to cause internal body temperature increase.

In their pioneering study on blood-brain barrier (BBB) permeability, Oscar and Hawkins exposed rats to MW at 1.3 GHz and analyzed BBB permeability by measuring uptake of several neutral polar substances in certain areas of the brain (Oscar and Hawkins 1977). A single, 20 min exposure, to continuous wave (CW) MW increased the uptake of D-mannitol at average power densities of less than 3 mW/ cm^2. Increased permeability was observed both immediately and 4 h after exposure, but not 24 h after exposure. After an initial rise at 0.01 mW/ cm^2, the permeability of cerebral vessels to saccharides decreased with increasing microwave power at 1 mW/cm^2. Thus, the effects of MW were observed within the power window of 0.01- 0.4 mW/cm^2. The findings on "power windows" for BBB permeability have been subsequently corroborated by the group of Persson and Salford (Salford, Brun et al. 1994; Persson, Salford et al. 1997). In their recent study, the effects of GSM MW on the permeability of the BBB and signs of neuronal damage in rats were investigated using a real GSM programmable mobile phone in the 900 MHz band (Eberhardt, Persson et al. 2008). The rats were exposed for 2 h at an SAR of 0.12, 1.2, 12, or 120 mW/kg.

Albumin extravazation and also its uptake into neurons increased after 14 d. The occurrence of dark neurons in the rat brains increased later, after 28 d. Both effects were seen already at 0.12 mW/kg with only slight increase, if any, at higher SAR values.

Sigmoid intensity dependences and power windows for the NT MW effects were observed in many other studies as previously reviewed (Postow and Swicord 1986; Grundler, Jentzsch et al. 1988; Golant 1989; Iskin 1990; Devyatkov, Golant et al. 1994; Blackman 2009).

Since 1980, there have been numerous reports of biological effects that show intensity "windows", that is, regions of intensity that cause changes surrounded by higher and lower intensities that show no effects from exposure, see for review (Blackman 2009). These results mean that lower intensity is not necessarily less bioactive, or less harmful.

Olcerst at al have reported that MW-induced increase in rubidium passive efflux did not increase monotonically with absorbed power (Olcerst, Belman et al. 1980). In fact, the highest exposure (SAR 390 mW/g) resulted in an increase, not statistically different from the lowest exposure level (SAR 100 mW/g) For sodium ions, at the greatest SAR of 390 mW/g, the effect was the smallest (Olcerst, Belman et al. 1980).

The data obtained in experiments with *E coli* cells and rat thymocytes provided new evidence for sigmoid type of PD dependence and suggested that, similar to ELF effects, MW effects may be observed within specific "intensity windows" (Belyaev, Shcheglov et al. 1992; Belyaev and Kravchenko 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997). The most striking example of the sigmoid PD dependence was found at the resonance frequency of 51.755 GHz (Belyaev, Shcheglov et al. 1996). When exposing *E. coli* cells at the cell density of $4 \cdot 10^8$ cell/ml, the effect reached saturation at the PD of 10^{-18}-10^{-17} W/cm^2 and did not change up to PD of 10^{-3} W/cm^2. In these experiments, the direct measurements of PD below 10^{-7} W/cm^2 were not available and lower PD was obtained using calibrated attenuators. Therefore, some uncertainty in the evaluation of the lowest PD was possible. The background MW radiation in this frequency range has been estimated to be 10^{-21}-10^{-19} W/m^2/Hz (Kolbun and Lobarev 1988). Based on the experimentally determined half-width of the 51.755 GHz resonance, 1 MHz (Belyaev, Shcheglov et al. 1996), the background PD was estimated as 10^{-19}-10^{-17} W/cm^2 within the 51.755 GHz resonance. The resonance MW effects on *E. coli* cells were observed at the PD very close to the estimated background value (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997; Shcheglov, Alipov et al. 2002). These data suggested that the PD dependence of MW effect at the specific resonance frequencies might have intensity threshold just slightly above the background level. Dependence of the MW effect on PD at one of the resonance frequencies, 51.675 GHz, had the shape of "intensity window" in the PD range

from 10^{-18} to 10^{-8} W/cm^2 (Shcheglov, Belyaev et al. 1997). It is interesting, that no MW effect at this resonance frequency was observed at sub-thermal and thermal PD. This type of PD dependence has supported hypothesis about possible rearrangement of the frequency MW spectra action by the MW field (Belyaev, Shcheglov et al. 1996). The position of the PD window varied between different resonance frequencies and depended on cell density during exposure of cells (Shcheglov, Belyaev et al. 1997). Despite some uncertainty in the evaluation of PD at the levels below 10^{-7} W/cm^2 in the referred studies the data indicated that NT MW at the resonance frequencies may result in biological effects at very low intensities comparable with intensities from base stations and other MW sources used in mobile communication.

Gapeev et al. have studied dependence of the MW effects at the resonance frequency of 41.95 GHz on the respiratory burst induced by calcium ionophore A23187 and PMA in the peritoneal neutrophils of mice (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). Inhibitory effects of MW exposure has been observed at the PD of 0.001 mW/cm^2 and displayed sigmoid dependence on PD at higher power densities (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). In other study, Gapeev et al. analyzed acute zymosan-induced paw edema in mice (Gapeyev, Mikhailik et al. 2009). MW exposure of animals at the frequency of 42.2GHz and exposure duration of 20 min decreased the paw edema. Sigmoid dependence of this effect on PD has been obtained with a maximum at the PD of 0.1 mW/cm^2.

French et al. exposed human astrocytoma cells to EMR at 835 MHz at a power density of either 40 mWcm^2 or 8.1 mWcm^2 (French, Donnellan et al. 1997). Lower power signal was more potent than high power signal. At the lower power density, it was observed that the rate of DNA synthesis decreased, and that the cells flattened and spread out in comparison to unexposed cultures. At higher power density there were no effects seen on cell proliferation, but alteration in cell morphology included increased cell spreading and also the appearance of actin-containing blebs at localized sites on the membrane. It was hypothesized that 835 MHz radiation at low power density may be affecting a signal transduction pathway involved in cell proliferation.

Sigmoid dependence of the negative impact of mobile phone usage on semen quality in human males was found in recent study analyzing motility, vitality, ROS generation by the whole cell, ROS generation by the mitochondria, oxidative DNA damage and DNA fragmentation (De Iuliis, Newey et al. 2009). Specifically, all of the responses examined showed an extremely rapid change at low SAR exposures that then reached a plateau at a point where around 30% of the sperm population was affected.

Hintzsche et al. have recently reported sigmoid dependence on PD in the range up to 4.3 mW/cm^2 for non-thermal effects of MW on mitotic spindle in human-hamster hybrid cells (Hintzsche, Jastrow et al. 2011).

Sun et al. have investigated the effects of exposure to a 1.8-GHz radiofrequency radiation (RFR) at different intensities on epidermal growth factor (EGF) receptor clustering and phosphorylation in human amniotic (FL) cells (Sun, Shen et al. 2012). The results showed that exposure to RFR at specific absorption rate (SAR) of 0.5, 1.0, 2.0, or 4.0 W/kg for 15 min significantly induced EGF receptor clustering and enhanced phosphorylation of the tyrosine-1173 residue in FL cells. The RFR effect displayed a sigmoid-dependence on SAR with a prominent plateau in the range of 0.5-4 W/kg and a threshold below 0.5 W/kg.

It should be mentioned that almost all biophysical mechanisms, which have previously been proposed to account for NT MW effects, predict thresholds in dependence of these effects in intensity (Grundler, Jentzsch et al. 1988; Golant 1989; Iskin 1990; Devyatkov, Golant et al. 1994; Golo 2005; Matronchik and Belyaev 2008).

To conclude, since 1970, there have been numerous reports of biological effects that show thresholds, sigmoid dependence of the NT MW effects on intensity and also "power windows", that is, regions of intensity that cause changes surrounded by higher and lower intensities that show no effects from exposure. These results mean that: (i) lower intensity is not necessarily less bioactive, or less harmful;(ii)the NT effects may be observed at intensities above thresholds which are very close to background levels and similar to intensities from base stations.

IV. DOSE AND DURATION OF EXPOSURE

So far, the "dose" (accumulated absorbed energy that is measured in radiobiology as the dose rate multiplied by exposure time) is not adopted for the MW exposures and PD or SAR (dose rate analog in radiobiology) is usually used for guidelines. To what degree SAR/PD can be applied to the nowadays NT MW chronic exposures is not exactly known and the current state of research demands reevaluation of the safety standards (Grigoriev, Nikitina et al. 2005).

Based on mechanistic consideration of the NT MW effects, Frey has suggested that the toxicology model used by investigators was not the appropriate model on which to design MW experiments (Frey 1993). With chemical substance in a toxicology model, a dose-response relationship is usually observed: the greater the dose, the greater the effect. In analogy with toxicology, MW experiments tended to be designed with high doses and with little regard for other parameters such

as modulation and frequency. This might be one reason why many MW studies yielded so little useful information (Frey 1993).

The role of exposure duration in combination with dose rate/SAR for appearance and persistence of the NT MW effects have been analyzed by many research groups using various end-points.

Koveshnikova et al. exposed rats to pulsed MW (carrier frequency 3 GHz, pulse repetition 400 Hz, rectangular pulses of 2 μs, power flux density , PD, of 100, 500 and 2500 μW/cm2), during 60 days, 12 h/daily (Koveshnikova and Antipenko 1991) (is a determining factor 1991b). Chromosomal abreactions (CA) were analyzed in hepatocytes. Exposure was performed at three arrays of pulses so that 16, 29 or 48 arrays of pulses per 1 min were generated. The ratio of the obtained doses per animal was 1 : 1.8 : 3, correspondingly. Increased level of CA was generally observed at PD > 100 $\mu W/cm^2$. Importantly, the differences between PD disappeared when the dose per animal increased. In particular, even the PD of 100 μW/cm2 induced CA at higher absorbed doses. These data support the notion that the absorbed dose may be an important parameter for estimation of risks.

Bozhanova with co-authors reported that the effect of cellular synchronization induced by NT MW depended on duration of exposure and PD (Bozhanova, Bryukhova et al. 1987). The dependence on duration of exposure fitted to exponential function. The important observation was that in order to achieve the same synchronization of cells, the decrease in PD could be compensated by the increase in the duration of exposure.

MW exposure of *E. coli* cells and rat thymocytes at PDs of 10^{-5}-10^{-3} W/cm^2 resulted in significant changes in chromatin conformation if exposure was performed at resonance frequencies during 5-10 min (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992; Belyaev and Kravchenko 1994). Decrease in the MW effects due to lowering the PD by orders of magnitude down to 10^{-14}-10^{-17} W/cm^2 could be compensated by several-fold increase of exposure time to 20-40 min (Belyaev, Alipov et al. 1994). At the relatively longer duration of exposure, more then 1 h, and the lowest PD of 10^{-19} W/cm^2, the same effect was induced as at highest PDs and shorter durations (Belyaev, Alipov et al. 1994).

Kwee and Raskmark analyzed effects of MW at 960 MHz and various SARs, 0.021, 0.21, and 2.1 mW/kg on proliferation of human epithelial amnion cells (Kwee and Raskmark 1998). These authors found linear correlations between exposure time to MW at 0.021 and 2.1 mW/kg and the MW-induced changes in cell proliferation albeit no such clear correlation was seen at 0.21 mW/kg.

Peinnequin et al. have studied effects of 24 or 48 h MW 2.45 GHz exposure at non-thermal level, 5 mW/cm^2, on apoptosis in human T-cell line Jurkat clone E6-1 (Peinnequin, Piriou et al. 2000). MW affected Fas -, but neither butyrate- nor ceramide - induced apoptosis. This effect depended on exposure time and was observed only upon 48 h exposure.

Croft et al. have tested twenty-four subjects participated in a single-blind fully counterbalanced cross-over design, where both resting EEG and phase-locked neural responses to auditory stimuli were measured while a mobile phone (MP) was either operating or turned off (Croft, Chandler et al. 2002). MP exposure altered resting EEG, decreasing 1-4 Hz activity (right hemisphere sites), and increasing 8-12 Hz activity as a function of exposure duration. MP exposure also altered early phase-locked neural responses, attenuating the normal response decrement over time in the 4-8 Hz band, decreasing the response in the 1230 Hz band globally and as a function of time, and increasing midline frontal and lateral posterior responses in the 30-45 Hz band. The data have shown that active MPs affect neural function in humans and do so as a function of exposure duration.

Caraglia et al. have evaluated the in vivo effect of MW-EMF in human epidermoid cancer KB cells (Caraglia, Marra et al. 2005). It was found that MW-EMF induced time-dependent apoptosis (45% after 3 h) that was paralleled by an about 2.5-fold decrease of the expression of ras and Raf-1 and of the activity of ras and Erk-1/2.

Gapeyev et al. studied anti-inflammatory effect of low-intensity MW exposure (0.1 mW/cm^2) using the model of acute zymosan-induced footpad edema in mice (Gapeyev, Mikhailik et al. 2008). Single whole-body MW exposure of mice at the frequencies of 42.2, 51.8, and 65 GHz after zymosan injection reduced both the footpad edema and local hyperthermia. At the frequency of 42.2 GHz the effect had sigmoid dependence on exposure duration with a maximum at 20-80 min. A linear dependence on the exposure duration with significantly lower increment was observed at a 10-fold less intensity (0.01 mW/cm^2). However, this decrease in the effect was compensated by a slight increase in duration of exposure from 80 min to 120 min.

Recently, the negative impact of mobile phone usage on semen quality in human males was repeatedly found to correlate with the duration of exposure (Agarwal, Deepinder et al. 2008; Agarwal, Desai et al. 2009).

Gerner et al. exposed human fibroblats to modulated GSM 1800 MHz at 2 W/kg (Gerner, Haudek et al. 2010). While short-term exposure within 2 hours did not significantly alter the proteome, an 8-h exposure caused a significant and reproducible increase in protein synthesis. Most of the proteins found to be induced were chaperones, which are mediators of protein folding. Heat-induced proteome alterations detectable with used proteome methodology would require heating

greater than 1°C. Because GSM-induced heating was less than 0.15°C, a heat-related response was excluded. These data further supported the notion that the exposure time seems to be a critical factor.

Differentiated astroglial cell cultures were exposed for 5, 10, or 20 min to either 900 MHz continuous waves or 900 MHz waves modulated in amplitude at 50 Hz (Campisi, Gulino et al. 2010). The strength of the electric field at the sample position was 10 V/m (rms). The irradiation conditions allowed the exclusion of any possible thermal effect. A significant increase in ROS levels and DNA fragmentation was found only after exposure of the astrocytes to modulated MW for 20 min. No evident effects were detected when shorter time intervals were used.

Adang et al. exposed Wistar albino rats to low-level RF during 21 months to two different microwave frequencies and exposure modes, 2 h a day, seven days a week (Adang, Remacle et al. 2009). After 14 and 18 months of exposure, the authors observed a significant increase in white blood cells and neutrophils of about 15% and 25%, respectively. Lymphocytes fell down after 18 months of exposure with about 15% compared to the sham-exposed group. No effects were observed at shorter duration of exposure. Exposure may probably have worked as a trigger and influenced the immune system, which reacted to this stressor by increasing the percentage of monocytes in the peripheral blood circulation.

Schrader et al. analysed production of spindle disturbances in FC2 cells, a human-hamster hybrid (A(L)) cell line, by MW with a field strength of 90 V/m at a frequency of 835 MHz (Schrader, Munter et al. 2008). Sigmoid dependence on time of exposure was observed with linear increase up to 30 min of exposure and saturation at longer exposures up to 2 h.

Markova et al. have found that inhibitory effect of MW on the 53BP1 foci leveled off at 1h-exposure (Markova, Malmgren et al. 2010). Human mesenchymal stem cells (MSC) and fibroblasts were expsosed to MW at GSM 915 MHz/UMTS 1947 MHz and SAR of 37/39 mW/kg. No further increase in effects was observed both in MSC and fibroblasts at prolongation of exposure to 3 h. This data are in agreement with previous results obtained in human peripheral blood lymphocytes that MW effects were the same at 1-h and 2-h exposures (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005).

Panagopoulos and Margaritis have studied the effects of different durations of a single (continuous), daily exposure, ranging from 1 min up to 21 min, to EMF from GSM 900 MHz (Global System for Mobile telecommunications) and DCS 1800 MHz (Digital Cellular System-referred to also as GSM 1800 MHz), on the reproductive capacity of Drosophila melanogaster (Panagopoulos and Margaritis 2010). The insects were exposed to each type of radiation at intensity of about 10 $\mu W/cm^2$, corresponding to a distance of 20 or 30 cm from the antenna of a DCS 1800 or

a GSM 900 mobile phone handset, respectively. The results show that the reproductive capacity decreases almost linearly with increasing exposure duration to both GSM 900 and DCS 1800 radiation, suggesting that short-term exposures to these radiations have cumulative effects. Additionally, the results show that GSM 900 MHz radiation is slightly more bioactive than DCS 1800 MHz radiation, at the same exposure durations and under equal radiation intensities.

In some studies, the prolonged MW exposures were associated with less prominent effects than shorter exposures (Nikolova, Czyz et al. 2005; Tkalec, Malaric et al. 2007; Markova, Malmgren et al. 2010). This type of dependence on exposure duration was explained by adaptation of the exposed biosystems to the MW exposure (Markova, Malmgren et al. 2010).

Esmekaya et al. exposed human peripheral blood lymphocyte to GSM modulated MW radiation at 1.8 GHz and SAR of 0.21 W/kg for 6, 8, 24 and 48 h (Esmekaya, Aytekin et al. 2011). The authors reported morphological changes in exposed lymphocytes. Longer exposure periods led to destruction of organelle and nucleus structures. Chromatin change and the loss of mitochondrial crista occurred in cells exposed to RF for 8 h and 24 h and were more pronounced in cells exposed for 48 h. RF exposure did not increase the temperature. The authors concluded that the greater damage occurred after longer periods of exposure to NT MW.

Tepe Çam and Seyhan have analyzed DNA damage in hair root cells of volunteers before and after they have used 900-MHz GSM mobile phone for 15 or 30 min. The 900-MHz GSM exposure significantly increased single-strand DNA breaks in cells of hair roots close to the position of phone at the heads of volunteers. 30 min talking by mobile phone induced more DNA damage than 15 min talking (Cam and Seyhan 2012).

Nazıroğlu et all have measured cytosolic free Ca^{2+} in human leukemia cells during 1-24 h exposure to 2.45 GHz electromagnetic radiation at the average SAR of 1.63 W/kg (Naziroglu, Cig et al. 2012). Radiation induced increase of cytosolic free Ca^{2+} concentration was time-dependent and was highest at 24-h exposure.

In some studies, prolonged MW exposures were associated with less prominent effects than shorter exposures (Nikolova, Czyz et al. 2005; Tkalec, Malaric et al. 2007; Markova, Malmgren et al. 2010). This type of dependence on exposure duration was accounted for adaptation of the exposed systems to the MW exposure. The magnitude of adaptation depends on a number of biological variables that will be considered elsewhere.

In recent German study, 24 out of 60 participants were exposed to MW from base station at a power density of < 60 μW/m², 20 participants to 60 - 100 μW/m², and 16 participants to more than 100 μW/m² (Buchner and Eger 2011). The values of the stress hormones adrenaline and noradrenaline grew significantly during the first 6 months after starting the GSM base station; the

values of the precursor substance dopamine substantially decreased in this time period. The initial condition was not restored even after 1.5 years. Due to the not regulable chronic difficulties of the stress balance, the phenylethylamine levels dropped until the end of the investigation period. These effects show a dose-effect relationship.

Recently reported general indications of a dose–response relationship between chronic exposure to cellular phone MW and parotid gland malignancy indicate necessity of the dose approach at the epidemiological level (Duan, Zhang et al. 2011). For the first time in epidemiology of RF-induced tumors, Cardis et al. have used estimates of radio frequency energy deposition at the centre of tumors in the brain as a measure of MW dose (Cardis, Armstrong et al. 2011). An increased risk of glioma was seen in individuals at the highest quintile of radio frequency dose, though reduced risks were seen in the four lower quintiles. When risk was examined as a function of dose received in different time windows before diagnosis, an increasing trend was observed with increasing MW dose (for exposures 7 years or more in the past.

In conclusion, the data from different groups suggest that duration of exposure and dose may have significant role for the NT MW effects. In specially designed studies, reduction in dose rate/SAR could be compensated by prolongation of exposure time in order to achieve the same MW effect. The temporal nature of the MW effects contributes to the apparent lack of consistent results reported in the literature. Emerging epidemiology data indicate that the dose of MW exposure may correlate with the increased brain tumor risk.

V. TIME AFTER EXPOSURE

The MW effects on *E. coli* cells significantly depended on the post-exposure time (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994; Shcheglov, Alipov et al. 2002). This dependence had an initial phase of increase about 100 min post-exposure followed by a phase, which was close to a plateau, around 100 min. A trend to decrease in effect was observed at longer times up to 300 min (Belyaev, Shcheglov et al. 1993; Shcheglov, Alipov et al. 2002).

Significant MW-induced changes in chromatin conformation were observed when rat thymocytes were analyzed in-between 30-60 min after exposure to MW (Belyaev and Kravchenko 1994). This effect nearly disappeared if the cells were incubated more than 80 min between exposure and analysis.

Gapeev et al. have studied dependence of the MW effect on the function of the mouse peritoneal neutrophils in dependence on duration of exposure at the frequency of 41.95 GHz and

the PD of 240 μW/cm^2 (Gapeev, Safronova et al. 1996; Gapeyev, Safronova et al. 1997). This dependence had a bell-shaped form with the maximal effects at 20 - 40 min of exposure.

In recent studies, human lymphocytes from peripheral blood of healthy and hypersensitive to EMF persons were exposed to NT MW from the GSM mobile phones (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005). NT MW induced changes in chromatin conformation similar to those induced by heat shock, which remained up to 24 h after exposure. It was found in the same and following studies that GSM MW at the carrier frequency of 915 MHz and UMTS (Universal Mobile Telecommunications System) MW at 1947.4 MHz inhibited formation of 53BP1/γ-H2AX DNA repair foci and these adverse effects remained during 72 h after an 1-h exposure (Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). The same group has reported that contrary to human fibroblast, which were able to adapt during chronic exposure to GSM/UMTS non-thermal MW, human stem cells did not adapt (Markova, Malmgren et al. 2010).

Jorge-Mora et al. investigated the effects of MW 2.45 GHz radiation on the paraventricular nucleus (PVN) of the hypothalamus, extracted from brains of exposed rats (Jorge-Mora, Misa-Agustino et al. 2011). Expression of c-Fos was analyzed in rats exposed once or repeatedly (ten times in 2 weeks) to MW at non-thermal SAR of 0.0776 and 0.301 W/kg. High SAR triggered an increase of the c-Fos marker 90 min or 24 h after radiation, and low SAR resulted in c-Fos counts higher than in control rats after 24 h. Repeated irradiation at 0.0776 W/kg increased cellular activation of PVN by more than 100% compared to animals subjected to acute irradiation and to repeated non-radiated repeated session control animals. The results suggest that the time of exposure to single or repeated doses of NT MW is a determining factor, though possibly not the only factor, in establishing the power levels that may produce a response.

Lu et al. have demonstrated that reactive oxygen species (ROS) plays an important role in the process of apoptosis in human peripheral blood mononuclear cell (PBMC), which is induced by the exposure to 900 MHz radiofrequency electromagnetic at the SAR of 0.4W/kg when the exposure lasts longer than two hours (Lu, Huang et al. 2012).

The data indicate that there is a time window for observation of the NT MW effects, which may be dependent on endpoint measured, cell type, duration and PD of exposure.

VI. COHERENCE TIME

MW exposure of L929 fibroblasts was performed by the group of Litovitz (Litovitz, Krause et al. 1993). MW at 915 MHz modulated at 55, 60, or 65 Hz approximately doubled ornithine

decarboxylase (ODC) activity after 8 h. Switching the modulation frequency from 55 to 65 Hz at coherence times of 1.0 s or less abolished enhancement, while times of 10 s or longer provided full enhancement. These results suggested that the microwave coherence effects are remarkably similar to those observed previously with extremely low frequency (ELF) magnetic fields by the same authors.

VII. INTERMITTENCE

Diem and colleagues exposed cultured human diploid fibroblasts and cultured rat granulosa cells to intermittent and continuous MW (1800 MHz; SAR 1.2 or 2 W/kg; different modulations; during 4, 16 and 24 h; intermittent 5 min on/10 min off or continuous exposure) (Diem, Schwarz et al. 2005). Comet assay was applied to analyze DNA single- and double-strand breaks. MW-induced effects occurred after 16 h exposure in both cell types and after different mobile-phone modulations. The intermittent exposure showed a stronger effect than continuous exposure.

Remondini et al. analyzed changes in gene expression in human HL-60 leukemia cells using gene microarrays (Remondini, Nylund et al. 2006). Cells were exposed to MW (SAR 1.0-1.3 W/kg, 1800 MHz DTX mode, 24 h exposure) either continuously or intermittently, 5 min ON/5 min OFF. Gene expression was affected by intermittent exposure but not continuous exposure.

Elhag et al. investigated effect of near field EMR from GSM mobile phones on the oxidant and antioxidant status in rats (Elhag, Nabil et al. 2007). Rats were subjected to either intermittent exposure (15 min/day for four days) or acute exposure for 1 h. Significant drop in the plasma concentration of vitamin C, vitamin E, vitamin A and reduced glutathione (GSH) was observed in both exposed groups as compared to controls. EMR exposure of rats produced a significant decrease in catalase (CAT) and superoxide dismutase (SOD) activities, with the values of these activities for acute-exposure group is significantly lower than those of intermittent exposure. The authors concluded that the effects of acute exposure to mobile phones on the rat's antioxidant status is significantly higher than those of intermittent exposure of the same type of radiation.

Chavdoula et al used a 6-min daily exposure of dipteran flies, Drosophila melanogaster, to GSM-900MHz (Global System for Mobile Telecommunications) mobile phone electromagnetic radiation (EMR), to compare the effects between the continuous and four different intermittent exposures of 6 min total duration on the insect's reproductive capacity as well as on the induction of apoptosis (Chavdoula, Panagopoulos et al. 2010). It was found that intermittent exposure, similar to continuous exposure, decreases the reproductive capacity and alters the actin-cytoskeleton network

of the egg chambers, another known aspect of cell death, and that this effect is due to DNA fragmentation. Intermittent exposures with 10-min intervals between exposure sessions proved to be almost equally effective as continuous exposure of the same total duration, whereas longer intervals between the exposures seemed to allow the organism the time required to recover and partly overcome the above-mentioned effects of the GSM exposure.

VIII. MODULATION

Several types of modulations used in mobile communication have previously been reviewed (Foster and Repacholi 2004; Blackman 2009; Juutilainen, Hoyto et al. 2011). In particular, the 2G signals use the Gaussian Minimum Shift Keying (GMSK) modulation, have a high coherence, extremely low frequency amplitude modulation spectra, high crest factor (pulsed signal) and a power regulation with an update in the order of seconds. In contrast, the 3G Wideband Code-Division Multiple Access (WCDMA) uses essentially Quadrature Phase Shift Keying (QPSK) modulation, has a low coherence and a broad-band extremely low frequency amplitude modulation spectrum.

While considering effect of modulation, all other parameters, which are important for appearance of biological effects induced by NT MW, should be taken into account. In particular it is useless to include in analysis the papers where no effects of NT MW were detected at all because usually these studies do not scan the parameters of exposure in wide range to enable detecting the NT MW effects. Even more importantly is to analyze separately different types of modulations because each type may result in its own specific effect. When such approach is used, clear evidence is emerging for the effects of specific modulations. For example, among three studies on cancer-relevant non-genotoxic endpoints, biological effects (apoptosis, altered cell proliferation, lipid peroxidation) were induced by GSM modulated signal but not by a CW signal (Juutilainen, Hoyto et al. 2011). All these studies involved combined exposure to RF fields and other agents, and found GSM-modulation-specific effects on apoptosis. Another example is increased power in the alpha band (8–12 Hz) of EEG, which has been consistently seen in several studies most of which have used GSM-type modulation and have found that signals with pulse modulation are more biologically active than CW fields, or that signals with higher degree of modulation (e.g., handset-like signals) are more biologically active than signals with lower degree of modulation (e.g., base station-like signals). Studies that have used only GSM-type signals have provided additional evidence for effects of modulated RF signals on human brain functions (van Rongen, Croft et al.

2009). Overall, the consistency of the positive findings indicates that there may be reproducible modulation-specific effects on the human central nervous system (Juutilainen, Hoyto et al. 2011). This result is consistent with the well-known notion that properly modulated RF may be a useful tool in experiments directed at understanding nervous system function (Frey 1967).

Using aforementioned approach, it became clear that significant body of papers where NT MW effects were observed and modulated and unmodlatlated signals were carefully compared revealed the differences. There is strong experimental evidence for the role of modulation in the diverse biological effects of NT MW both in vitro and in vivo (Lin-Liu and Adey 1982; Byus, Lundak et al. 1984; Dutta, Subramoniam et al. 1984; Byus, Kartun et al. 1988; Dutta, Ghosh et al. 1989; Veyret, Bouthet et al. 1991; Gapeev, Iakushina et al. 1997; Litovitz, Penafiel et al. 1997; Penafiel, Litovitz et al. 1997; Persson, Salford et al. 1997; d'Ambrosio, Massa et al. 2002; Huber, Treyer et al. 2002; Markkanen, Penttinen et al. 2004; Huber, Treyer et al. 2005). Examples include different types of modulation such as amplitude-, speech and phase modulations: (i) Amplitude modulation at 16 Hz, but not 60 Hz or 100 Hz, of a 450-MHz MW increased activity of ODC (Byus, Kartun et al. 1988). (ii) Speech-modulated 835-MHz MW produced no effect on ODC as compared to the typical signal from a TDMA (Time Division Multiple Access) digital cellular phone (Penafiel, Litovitz et al. 1997). (iii) Phase-modulated GSM-1800 MW (Gaussian Minimum Shift Keying, GMSK) at 1.748 GHz induced micronuclei in human lymphocytes while CW MW did not (d'Ambrosio, Massa et al. 2002).

Normal human lymphocytes were exposed for 5 days to continuous wave (CW) or pulsed wave (PW) 2450-MHz radiation at non-heating (37 degrees C) and various heating levels (temperature increases of 0.5, 1.0, 1.5, and 2 degrees C) (Czerska, Elson et al. 1992). The pulsed exposures involved 1-microsecond pulses at pulse repetition frequencies from 100 to 1,000 pulses per second at the same average SAR levels as the CW exposures. At non-heating levels, CW exposure did not affect lymphoblastoid transformation. At heating levels both conventional and CW heating enhanced transformation to the same extent and correlate with the increases in incubation temperature. PW exposure enhanced significantly transformation at non-heating levels. At heating levels PW exposure enhanced transformation to a greater extent than did conventional or CW heating. Authors concluded that PW 2450-MHz radiation acts differently on the process of lymphoblastoid transformation in vitro compared with CW 2450-MHz radiation at the same average SARs.

Bolshakov and Alexeeev used microelectrode and voltage-clamp techniques to record spontaneous electrical activity and ionic currents of Lymnea stagnalis neurons during exposure to a 900-MHz field in a waveguide-based apparatus (Bolshakov and Alekseev 1992). The field was

pulse-modulated at repetition rates ranging from 0.5 to 110 pps, or it was applied as a continuous wave (CW). When subjected to pulsed waves (PW), rapid, burst-like changes in the firing rate of neurons occurred at SARs of a few W/kg. If the burst-like irregularity was present in the firing rate under control conditions, irradiation enhanced its probability of occurrence. The effect had a threshold SAR near 0.5 W/kg. CW radiation had no effect on the firing rate pattern at the same SAR. Thus, the effect was dependent on modulation. Mediator-induced, current activation of acetylcholine, dopamine, serotonin, or gamma-aminobutyric-acid receptors of the neuronal soma was not altered during CW or PW exposures and, hence, could not have been responsible for the bursting effect.

Gapeev and co-authors studied production of reactive oxygen species (ROS) in isolated peritoneal neutrophils of mice using a model of synergistic reaction of calcium ionophore A23187 and phorbol ester PMA (Gapeev, Iakushina et al. 1997; Gapeyev, Yakushina et al. 1998). MW exposure at 41.95 GHz, continuous wave mode and 50 $\mu W/cm^2$, inhibited ROS production. MW modulated with the frequency of 1 Hz resulted in stimulation of the synergistic reaction. Modulation frequencies of 0.5, 2, 4, and 8 Hz did not cause significant effects, and modulation frequencies of 0.1, 16, and 50 Hz inhibited the synergistic reaction.

In other study, Gapeev et al. analyzed acute zymosan-induced paw edema in mice (Gapeyev, Mikhailik et al. 2009). MW exposure of animals at the PD of 0.1- 0.7 mW/cm^2 and some "effective" frequencies in the range of 42-43 GHz decreased the paw edema. Application of different modulation frequencies from the range of 0.03–100 Hz to MW exposure at the effective carrier frequency of 42.2 GHz did not lead to considerable changes in the effect. In contrast, modulation of MW at the ''ineffective'' carrier frequencies of 43.0 and 61.22 GHz by frequencies from the ranges of 0.07–0.1 and 20–30 Hz resulted in a maximal anti-inflammatory effects. The results suggested a complex dependence of the anti-inflammatory action of low-intensity MW on carrier and modulation frequencies.

Capri et al. evaluated the nonthermal effects of both a 900 MHz GSM signal and a 900 MHz CW RF field at low SARs (70–76 mW/kg average) on human peripheral blood mononuclear cells (PBMCs) *in vitro* (Capri, Scarcella et al. 2004). Data obtained from cells exposed to a GSM-modulated RF field showed a slight decrease in cell proliferation when PBMCs were stimulated with the lowest mitogen concentration and a slight increase in the number of cells with altered distribution of phosphatidylserine across the membrane. Data obtained from CW-exposed cultures showed no difference with respect to sham-exposed cultures in any of the end points studied.

Huber with coauthors investigated effects of MW similar to those used in mobile communication, a "base-station-like" and a "handset-like" signal (10 g tissue-averaged spatial peak-

SAR of 1 W/kg for both conditions), on waking regional cerebral blood flow (rCBF) in 12 healthy young men (Huber, Treyer et al. 2005). The effect depended on the spectral power in the amplitude modulation of the carrier frequency such that only "handset-like" MW exposure with its stronger low-frequency components but not the "base-station-like" MW exposure affected rCBF. This finding supported previous observations of these authors (Huber, Treyer et al. 2002) that pulse modulation of MW is of importance for changes in the waking and sleep EEG, and substantiated the notion that pulse modulation is crucial for MW-induced alterations in brain physiology.

Markkanen et al. exposed cdc48-mutated *Saccharomyces cerevisiae* yeast cells to 900 or 872 MHz MW, with or without exposure to ultraviolet (UV) radiation, and analyzed apoptosis (Markkanen, Penttinen et al. 2004). Amplitude modulated (217 pulses per second) MW significantly enhanced UV induced apoptosis in cells, but no effect was observed in cells exposed to unmodulated fields at the identical time-average SAR of 0.4 W/kg that was lower than the ICNIRP safety standards.

Persson and colleagues studied effects of MW of 915 MHz as CW and pulse-modulated with different pulse power and at various time intervals on permeability of the blood-brain barrier (BBB) in Fischer 344 rats (Persson, Salford et al. 1997). Albumin and fibrinogen were demonstrated immunochemically and classified as normal versus pathological leakage. The CW-pulse power varied from 0.001 W to 10 W and the exposure time from 2 min to 960 min. The frequency of pathological rats significantly increased in all exposed rats. Grouping the exposed animals according to the level or specific absorption energy (J/kg) gave significant difference in all levels above 1.5 J/kg. The exposure was 915 MHz MW either pulse modulated at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width, or CW. The frequency of pathological rats was significantly higher in MW-exposed groups than in controls and the frequency of pathological rats after exposure to pulsed radiation was significantly less than after exposure to CW.

In a study by Lypez-Martin et al. (Lopez-Martin, Brogains et al. 2009), GSM-exposed picrotoxin-pretreated rats showed differences in clinical and EEG signs, and in c-Fos expression in the brain, in comparison to picrotoxin-treated rats exposed to an equivalent dose of unmodulated radiation. Neither MW exposure caused tissue heating, so thermal effects could be ruled out. The most marked effects of GSM MW on c-Fos expression in picrotoxin-treated rats were observed in limbic structures, olfactory cortex areas and subcortical areas, the dentate gyrus, and the central lateral nucleus of the thalamic intralaminar nucleus group. Nonpicrotoxin-treated animals exposed to unmodulated radiation showed the highest levels of neuronal c-Fos expression in cortical areas. These results suggested a specific effect of the pulse GSM modulation on brain activity of a picrotoxin-induced seizure-proneness rat model.

Luukkonen et al. investigated effects of MW at 872 MHz and relatively high SAR value (5 W/kg) on intracellular reactive oxygen species (ROS) production and DNA damage in human SH-SY5Y neuroblastoma cells. The experiments also involved combined exposure to MW and menadione, a chemical inducing intracellular ROS production and DNA damage. Both CW and a pulsed signal similar to that used in GSM mobile phones were used. Exposure to the CW radiation increased DNA breakage in comparison to the cells exposed only to menadione. Comparison of the same groups also showed that ROS level was higher in cells exposed to CW RF radiation at 30 and 60 min after the end of exposure. No effects of the GSM-like modulated signal were seen on either ROS production or DNA damage.

Hinrikus et al. (Hinrikus, Bachmann et al. 2008) evaluated the effects of MW (450 MHz) pulse-modulated at the frequencies of 7, 14 and 21 Hz on human electroencephalographic (EEG) rhythms. The field power density at the scalp was 0.16 m W/cm^2. Modulated microwaves caused an increase in the average EEG alpha (17%) and beta (7%) power but the theta rhythm remained unaffected. Increases in the EEG alpha and beta power were statistically significant during the first half-period of the exposure interval (30 s) at the modulation frequencies of 14 and 21 Hz. The authors concluded that the effect of the 450-MHz MW modulated at 7, 14 and 21 Hz varies depending on the modulation frequency.

Hoyto et al. exposed human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells to MW (SAR of 5 W/kg) at 872 MHz using continuous-waves (CW) or a modulated GSM-like signal under isothermal conditions (Hoyto, Luukkonen et al. 2008). Menadione was used to induce reactive oxygen species, and tert-butylhydroperoxide (t-BOOH) was used to induce lipid peroxidation. Two statistically significant differences related to MW exposure were observed: Lipid peroxidation induced by t-BOOH was increased in SH-SY5Y (but not in L929) cells, and menadione-induced caspase 3 activity was increased in L929 (but not in SH-SY5Y) cells. Both differences were statistically significant only for the GSM-modulated signal.

Franzellitti et al. exposed human trophoblast HTR-8/SVneo cells to MW at 1.8 GHz CW and differently modulated GSM signals (GSM-217Hz, (speaking only): and GSM-Talk (34% of speaking and 66% of hearing):) during 4 - 24 h (Franzellitti, Valbonesi et al. 2008). The inducible HSP70C transcript was significantly enhanced after 24 h exposure to GSM-217 Hz signals while being reduced after 4 and 16 h exposure to GSM-Talk signal. In another study of the same group , HTR-8/SVneo cells were exposed for 4, 16 or 24 h to 1.8 GHz continuous wave (CW) and different GSM signals, namely GSM-217 Hz and GSM-Talk (intermittent exposure: 5 min field on, 10 min field off). The alkaline comet assay was used to evaluate primary DNA damages and/or strand breaks due to uncompleted repair processes in HF-EMF exposed samples. The amplitude-

modulated signals GSM-217 Hz and GSM-Talk induced a significant increase in comet parameters in trophoblast cells after 16 and 24 h of exposure, while the un-modulated CW was ineffective (Franzellitti, Valbonesi et al. 2010).

Only CW RF resulted in statistically significant effect on immune system of the exposed rats (Campisi, Gulino et al. 2010). In this study, primary rat neocortical astroglial cell cultures were exposed to MW for 5, 10, or 20 min to either 900 MHz continuous waves or 900 MHz waves modulated MW in amplitude at 50 Hz using a sinusoidal waveform and 100% modulation index. The strength of the electric field (rms value) at the sample position was 10 V/m. A significant increase in ROS levels and DNA fragmentation was found only after exposure of the astrocytes to modulated EMF for 20 min. No evident effects were detected when shorter time intervals or continuous waves were used. The irradiation conditions allowed the exclusion of any possible thermal effect. The results show the importance of the amplitude modulation in the interaction between EMF and neocortical astrocytes (Campisi, Gulino et al. 2010).

There are studies where similar effects of modulated and CW MW were observed. Adang et al. exposed Wistar albino rats to low-level CW and pulse-amplitude modulated RF during 21 months at 970 MHz (Adang, Remacle et al. 2009). Similar effects on immune system were observed in both groups.

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 (Grigoriev, Stepanov et al. 2003). 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 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 on the role of modulation on MW effects is available in English (Pakhomov and Murphy 2000). The 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". Since that time, more studies have been published in Russian which show the role of modulation in experiemnts with animals (Dolgacheva, Semenova et al. 2000; Pashovkina and Akoev 2000; Pashovkina and Akoev 2001; Pashovkina and Akoev 2001; Akoev, Pashovkina et al. 2002).

In conclusion, significant amount of in vitro and in vivo studies from different research groups, although not universally reported, clearly indicated dependence of the NT MW effects on modulation.

IX. POLARIZATION

Polarization is a property of electromagnetic waves that describes the orientation of their oscillations versus direction of propagation. In most cases, electromagnetic wave propagates in free space as a transverse wave - the polarization is perpendicular to the wave's direction of propagation. The electric field may be oriented in a single direction (linear polarization), or it may rotate as the wave propagates (circular or elliptical polarization). In the latter cases, the oscillations can rotate either towards the right (right-handed polarization) or towards the left (left-handed polarization) in the direction of propagation.

The effects of circularly polarized (CP) MW were studied in *E. coli* cells at the frequencies from two frequency windows (resonances) that were identified using linearly polarized (LP) MW, within the frequency ranges of 51.62-51.84 GHz and 41.25-41.50 GHz (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992). At the resonance frequency of 51.76 GHz, right-handed CP MW inhibited repair of X-ray-induced DNA damages (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992). In contrast to right-handed polarization, left-handed CP MW had virtually no effect on the DNA repair, while the efficiency of LP MW was in-between of two circular polarizations. Inversion in effectiveness of circular polarizations was observed at another resonance frequency, 41.32 GHz. In contrast to the frequency of 51.76 GHz, left-handed CP MW at 41.32 GHz significantly inhibited DNA repair, while right polarization was almost ineffective. MW of the same CP affected cells at several frequencies tested within each resonance, alternative CP being almost ineffective (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992; Belyaev, Shcheglov et al. 1992). Therefore, specific sign of effective CP, either left- or right-, was the attribute of each resonance. Two different types of installations, based on either spiral waveguides (Belyaev, Shcheglov et al. 1992) or quarter-wave mica plates (Belyaev, Alipov et al. 1992; Belyaev,

Shcheglov et al. 1992; Shcheglov, Belyaev et al. 1997; Ushakov, Shcheglov et al. 1999; Ushakov, Alipov et al. 2005), were used to produce CP MW. Similar results were observed regardless the way of producing the MW of different polarizations.

Pre-irradiation of *E. coli* cells to X-rays inverted the sign of effective polarization (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992). This inversion was observed for two different resonances, 41.32 and 51.76 GHz. Neither resonance frequencies, nor half-widths of the resonance changed during the inversions in effective CPs. The effects of left- and right-handed CP MW become the same at 50 cGy (Belyaev, Alipov et al. 1992). At this dose, about one single stranded DNA break per haploid genome was induced. X-ray-induced DNA breaks result in relaxation of the supercoiled DNA-domains. It is known that the majority of DNA in living cells has a right-handed helicity (B-form) but a minor part, in order of 1 %, may alternate from the B-form with the form of left-handed helix (Z-form). Supercoiling is connected with transitions between right B-form to left Z-form in these DNA sequences. Therefore, the data suggested that difference in biological effects of polarized MW might be connected with DNA helicity and supercoiling of DNA-domains.

Supercoiling of DNA-domains is changed during cell cycle because of transcription, replication, repair, and recombination. It can also be changed by means of DNA-specific intercalators such as ethidium bromide (EtBr). EtBr changes supercoiling and facilitates the transition of DNA sequences from Z-form to B-form. Preincubation of *E. coli* AB1157 cells with EtBr inverted the effective polarization at the resonance frequency of 51.755 GHz and right-handed MW became more effective than left polarization (Ushakov, Shcheglov et al. 1999). EtBr changed the supercoiling of DNA-domains starting at a concentration of 1 μg/ml as measured with the AVTD in different cell types including *E. coli* (Belyaev, Shcheglov et al. 1996; Belyaev, Alipov et al. 1997; Belyaev, Eriksson et al. 1999). These data provided further evidence that DNA may be a target for the NT MW effects.

The effects of MW on conformation of nucleoids in *E. coli* cells have recently been studied at the power flux density of 100 $\mu W/cm^2$ (Ushakov, Alipov et al. 2006). Linearly polarized MW resulted in significant effects within specific frequency windows of resonance type in the range of 51-52 GHz. The distances between frequency windows were about 55-180 MHz. Only one of the two possible circular polarizations, left-handed or right-handed, was effective at each frequency window. The sign of effective circular polarization alternated between frequency windows.

While most data on the role of polarization in MW effects on chromatin have been obtained by the same research group (Belyaev, Alipov et al. 1992; Belyaev, Shcheglov et al. 1992; Belyaev, Shcheglov et al. 1992; Alipov, Belyaev et al. 1993; Belyaev, Alipov et al. 1993; Belyaev, Shcheglov et al. 1993; Belyaev and Kravchenko 1994; Shcheglov, Belyaev et al. 1997; Ushakov,

Shcheglov et al. 1999; Ushakov, Alipov et al. 2005; Ushakov, Alipov et al. 2006), recent data of others corroborated our findings at least partially (Shckorbatov, Pasiuga et al. 2009). These authors analyzed the condensation of chromatin in human buccal epithelium cells and human fibroblasts by the method of vital indigo carmine staining. MW induced chromatin condensation in dependence on polarization (Shckorbatov, Pasiuga et al. 2009). The same research group investigated the effects influence of linear and left-handed and right-handed elliptically polarized MW at 36.65 GHz on chromatin in human fibroblast nuclei (Shckorbatov, Pasiuga et al. 2010). Microwave irradiation at 10 and 100 $\mu W/cm^2$ induced chromatin condensation. The right-handed elliptically polarized radiation was more active than the left-handed polarization.

Obviously, the difference in effects of right- and left polarizations could not be explained by the heating or by the mechanism dealing with "hot-spots" due to unequal SAR distribution. The data about the difference in effects of differently polarized MW, the inversion of effective circular polarization between resonances and after irradiation of cells with X-rays and incubation with EtBr provided strong evidence for the non-thermal mechanisms of MW effects. These data suggested chiral asymmetry in the target for the NT MW effects, one of which is presumably chromosomal DNA (Belyaev, Alipov et al. 1992), and selection rules on helicity if quantum-mechanical approach is applied (Belyaev, Shcheglov et al. 1992).

Lai and Singh have consistently reported that circularly polarized MW exposure at 2450 MHz induced DNA damage in brain cells of the exposed rats (Lai and Singh 1995; Lai and Singh 1996; Lai and Singh 1997). Replication studies have also tested circularly polarized MW exposure at 2450 MHz and no induced DNA damage was reported (Malyapa, Ahern et al. 1997; Malyapa, Ahern et al. 1998; Lagroye, Anane et al. 2004). All these replication studies have used another exposure system. However, handedness of circular polarization has not been described neither in original study, no in replications. If the handedness was different between studies it could reasonably account for inconsistency.

In some studies, MW of circular polarization with undefined handedness were used, but the obtained effects were not compared with alternative circular polarization or linear polarization (Bartsch, Kupper et al. 2010).

XI. ELECTROMAGNETIC ENVIRONMENT

It is very likely that background EMF might be of importance for the MW effects. This hypothesis is based on the experimental observations that SMF, ELF magnetic fields, and MW at

low intensities induced similar effects in cells under specific conditions of exposure (Belyaev, Alipov et al. 1999; Belyaev, Shcheglov et al. 2000; Belyaev and Alipov 2001; Binhi, Alipov et al. 2001; Belyaev, Hillert et al. 2005). Despite very little has been achieved for mechanistic explanation of such effects, there are attempts to consider the effects of EMF in a wide frequency range in the frames of the same physical models (Chiabrera, Bianco et al. 1991; Matronchik, Alipov et al. 1996; Chiabrera, Bianco et al. 2000; Binhi 2002; Panagopoulos, Karabarbounis et al. 2002; Matronchik and Belyaev 2005; Matronchik and Belyaev 2008).

Litovitz and colleagues found that the ELF magnetic noise inhibited the effects of MW on ODC in L929 cells (Litovitz, Penafiel et al. 1997). The ODC enhancement was found to decrease exponentially as a function of the noise root mean square amplitude. With 60 Hz amplitude-modulated MW, complete inhibition was obtained with noise levels at or above 2 μT. With the DAMPS (Digital Advanced Mobile Phone System) cellular phone MW, complete inhibition occurred with noise levels at or above 5 μT. Further studies by the same group revealed that the superposition of ELF noise inhibited hypoxia de-protection caused by long term repeated exposures of chick embryos to MW (Di Carlo, White et al. 2002).

The effect of a magnetic noise on microwave-induced spatial learning deficit in the rat was investigated by Lai (Lai 2004). Rats were exposed to MW (2450 MHz CW, PD 2 mW/cm^2, average whole-body SAR 1.2 W/kg) alone or in combination with noise exposure (60 mG). Microwave-exposed rats had significant deficit in learning. Exposure to noise alone did not significantly affect the performance of the animals. However, simultaneous exposure to noise significantly attenuated the microwave-induced spatial learning deficit. The author concluded that simultaneous exposure to a temporally incoherent magnetic field blocks MW-induced spatial learning and memory deficits in the rat (Lai 2004).

Lai and Singh studied combined effects of a temporally incoherent magnetic noise (45 mG) and MW (CW 2450 MHz, PD 1 mW/cm^2, average whole-body SAR of 0.6 W/kg) in rat brain cells (Lai and Singh 2005). MW exposure induced significant DNA breakages as measured with both neutral and alkaline comet assays. Exposure to noise alone did not significantly affect cells. However, simultaneous noise exposure blocked the MW-induced effects.

Burch et al. have analyzed the relationship between cellular telephone use and excretion of the melatonin metabolite 6-hydroxymelatonin sulfate (6-OHMS) in two populations of male electric utility workers (Study 1, *n*=149; Study 2, *n*=77) (Burch, Reif et al. 2002). Participants collected urine samples and recorded cellular telephone use over 3 consecutive workdays. Personal 60-Hz magnetic field (MF) and ambient light exposures were characterized on the same days. A repeated measures analysis was used to assess the effects of cellular telephone use, alone and combined with

MF exposures, after adjustment for age, participation month and light exposure. No change in 6-OHMS excretion was observed among those with daily cellular telephone use >25 min in Study 1 (5 worker-days). Study 2 workers with >25 min cellular telephone use per day (13 worker-days) had lower creatinine-adjusted mean nocturnal 6-OHMS concentrations (p=0.05) and overnight 6-OHMS excretion (p=0.03) compared with those without cellular telephone use. There was also a linear trend of decreasing mean nocturnal 6-OHMS/creatinine concentrations (p=0.02) and overnight 6-OHMS excretion (p=0.08) across categories of increasing cellular telephone use. A combined effect of cellular telephone use and occupational 60-Hz MF exposure in reducing 6-OHMS excretion was also observed in Study 2. The authors concluded that exposure-related reductions in 6-OHMS excretion were observed in Study 2, where daily cellular telephone use of >25min was more prevalent. Prolonged use of cellular telephones may lead to reduced melatonin production, and elevated 60-Hz MF exposures may potentiate the effect.

Yao and colleagues investigated the influence of the GSM-like MW at 1.8 GHz on DNA damage and intracellular reactive oxygen species (ROS) formation in human lens epithelial cells (hLECs) (Yao, Wu et al. 2008). DNA damage examined by alkaline comet assay was significantly increased after 3 W/kg and 4 W/kg radiation, whereas the double-strand breaks (DSB) evaluated by γ-H2AX foci were significantly increased only after 4 W/kg radiation. Significantly elevated intracellular ROS levels were detected in the 3-W/kg and 4-W/kg groups. After exposure to 4 W/kg for 24 hours, hLECs exhibited significant G_0/G_1 arrest. All the effects were blocked when the MW exposure was superposed with a 2 μT electromagnetic noise. The authors concluded that superposed electromagnetic noise blocks MW-induced DNA damage, ROS formation, and cell cycle arrest.

It has previously been reported that resonance effects of MW on *E. coli* cell depend on the magnitude of static magnetic field at the place of MW exposure (Belyaev, Alipov et al. 1994). This dependence was explained by the model of electron-conformational interactions that also predicted possible shift of resonance frequencies in dependence on SMF (Belyaev, Shcheglov et al. 1996).

More recently, Ushakov with co-authors exposed *E. coli* cells to MW at the PD of 10^{-10} W/cm^2 and the frequencies of 51.675, 51.755 and 51.835 GHz (Ushakov, Alipov et al. 2005). In this study, cells were exposed to MW at various values of SMF within the range of geomagnetic filed: 22, 49, 61, or 90 μT. The authors observed that the effects of MW exposure on the conformation of nucleoids depended on the SMF during exposure.

Gapeev at al. analyzed effects of MW (41.85-42.1 GHz, frequency increment 50 MHz, PD 50 μВт/cm^2, 20 min exposure) on synergistic reaction of calcium ionophore A23187 and phorbol ester PMA in activation of the respiratory burst of the peritoneal neutrophils of mice (Gapeev,

Iakushina et al. 1997). The MW exposure was performed at various SMF. At a SMF of 50 μT, the authors observed frequency-dependent inhibition of the synergetic reaction with maximal effect at the frequency of 41.95 GHz. In the same frequency range, frequency-dependent activation of the synergetic reaction with a maximal effect at the frequency of 42.0 GHz was found at a SMF of 95 μT. The authors concluded that increasing the SMF from 50 to 95 μT resulted in the inversion of ten MW effects and the shift of the resonance frequency by 50 MHz (Gapeev, Iakushina et al. 1997; Gapeev, Iakushina et al. 1999). Moreover, these effects of MW at the 41.95 GHz and 42.0 GHz were not found at the SMF of ±1, 28.3, 75.5 or 117.3 μT suggesting that the NT MMW effects may appear only at specific values of SMF (Gapeev, Iakushina et al. 1997; Gapeev, Iakushina et al. 1999).

During 1997–2008, Bartsch et al. have performed two long-term (I and II) and two life-long (III and IV) experiments analyzing the effect of chronic exposure to a low-intensity GSM-like signal (900 MHz pulsed with 217 Hz, 100 μW/cm² average power flux density, 38–80 mW/kg SAR for whole body) on health and survival of unrestrained female Sprague-Dawley rats kept under identical conditions (Bartsch, Kupper et al. 2010). Radiofrequency continued up to 37 months. In experiment I no adverse health effects of chronic RF-exposure were detectable, neither by macroscopic nor detailed microscopic pathological examinations. Also in experiment II no apparent macroscopic pathological changes due to treatment were apparent. In the course of two complete survival experiments (2002–2005; 2005–2008) median survival was significantly shortened under RF-exposure in both experiments by 9.06% (95% CI 2.7 to 15.0%) (p=0.0064); i.e by 72 days in experiment III and 77 days in experiment IV (Bartsch, Kupper et al. 2010). Based on their thorough analysis of possible reasons for variability in RF effects from year to year, the authors assumed that theses variations follow the course of solar activity within the 11-years' sunspot cycle which, according to theirs reported observations, seems to affect pineal melatonin secretion which is an integral part of endogenous defense against cancer. The activity of the sun may influence laboratory animals via changes in the geomagnetic field, which is omnipresent and perceived by specific receptors, e.g. retinal melanopsin, also involved in the light-mediated synchronization of the SCN (central circadian clock of the brain) and controlling the circadian secretion of pineal melatonin.

The observations indicating dependence of the NT MW effects on SMF and EMF stray field may be of significant interest for further development of physical theory for the NT MW effects and development of safe mobile communication.

XII. CELL-TO-CELL INTERACTION IN RESPONSE TO MICROWAVES

The effects of NT MW at the resonance frequency of 51.755 GHz on conformation of nucleoids in *E. coli* cells were analyzed with respect to cell density during exposure (Belyaev, Alipov et al. 1994). The per-cell-normalized effect of MW increased by a factor of 4.7±0.5 on average if cell density increased by one order of magnitude, from $4 \cdot 10^7$ to $4 \cdot 10^8$ cell/ml. These data suggested a co-operative nature of cell response to MW, which is based on cell-to-cell interaction during exposure. This suggestion was in line with the observed partial synchronization of cells after exposure to MW.

The co-operative nature of cell response to MW at the resonance frequency of 51.755 GHz was confirmed in further studies with *E. coli* cells (Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997; Shcheglov, Alipov et al. 2002). In addition, dependence of the per-cell-normalized effect on cell density was found for two other resonances, 51.675 GHz and 51.688 GHz. These data suggested that dependence on cell density during exposure is a general attribute of the resonance response of *E. coli* cells to NT MW. At the cell density of $4 \cdot 10^8$ cells/ml, the average intercellular distance was approximately 13 μm that is 10 times larger than the linear dimensions of *E. coli* cells (Belyaev, Alipov et al. 1994; Shcheglov, Alipov et al. 2002). Therefore, no direct physical contact seemed to be involved in the cell-to-cell interaction. Two mechanisms, biochemical and electromagnetic, were considered to account for the co-operative nature in the resonance response to weak EMF in wide frequency range including ELF, MW and ionizing radiation (Belyaev 1993; Belyaev, Alipov et al. 1994; Alipov, Shcheglov et al. 2003). The first one, biochemical, is based on release of secondary chemical messengers (ions, radicals, or molecules) by those cells, which were directly targeted. Via diffusion, these messengers can induce response in other cells. The second mechanism, electromagnetic, is based on reemission of secondary photons. According to this mechanism, reemitted photons can induce response in other cells if the intercellular distance is shorter than the length of photon absorption. The experimental data on MW effects fitted better to the electromagnetic mechanism but a combination of two mechanisms was also possible (Belyaev, Alipov et al. 1994; Shcheglov, Alipov et al. 2002). In particular, radicals with prolonged lifetimes might be involved in the observed cell-to-cell communication during response to EMF (Belyaev, Alipov et al. 1998).

The absorption length of photons with the frequencies of 10^{12}-10^{13} Hz corresponds to the intracellular distance at the cell density of $5 \cdot 10^8$ cell/ml, at which saturation in the dependences of EMF effects on cell density was observed (Belyaev, Alipov et al. 1994; Belyaev, Alipov et al. 1995; Belyaev, Alipov et al. 1998; Shcheglov, Alipov et al. 2002). Such photons may be involved in cell-

to-cell communication according to the electromagnetic mechanism and in agreement with the prediction of Fröhlich that biosystems support coherent excitations within frequency range of 10^{11}-10^{12} Hz (Frohlich 1968). From this point of view, cell suspension may respond to NT MW as a whole. In this case, the number of the exposed cells should be large enough to facilitate cell-to-cell communication during the responses to MW at specific parameters of exposure such as frequency, modulation, and polarization. Interestingly, the cell density for saturation of both MW and ELF effects was about $5 \cdot 10^8$ cell/ml that is close to cell densities in soft tissues of eukaryotes (Belyaev, Alipov et al. 1998; Shcheglov, Alipov et al. 2002). Such density of cells in the tissues may be important for regulation of living systems by electromagnetic cell-to-cell communication. Cellular membranes and DNA have been considered as possible sources of coherent excitations and photons, which may be involved in electromagnetic cell-to-cell communication (Frohlich 1968; Belyaev, Shcheglov et al. 1996; Belyaev, Alipov et al. 1998).

PD dependences of the MW effect at the 51.755 GHz resonance frequency were considerably different between two cell densities, $4 \cdot 10^7$ cells/ml and $4 \cdot 10^8$ cells/ml (Belyaev, Shcheglov et al. 1996). However, the resonance frequency of 51.755 GHz did not shift with the changes in cell density. The half-width of the 51.755 GHz resonance did not depend on cell density either. Contrary to the 51.755 GHz resonance response, the half-width of the 51.675 GHz resonance depended on cell density (Shcheglov, Belyaev et al. 1997). The data suggested that intracellular interaction during the NT MW exposures at some specific frequencies might affect sub-cellular targets for NT MW. This target is presumably chromosomal DNA that is organized in the DNA-domains (Belyaev, Alipov et al. 1992; Belyaev, Alipov et al. 1993; Matronchik and Belyaev 2005).

In all studies concerning dependence of the MW effects on cell density, the cells occupied a negligible part of the exposed volume and could not change the absorption of MW even at the highest cell densities (Belyaev, Alipov et al. 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997; Shcheglov, Alipov et al. 2002). Striking difference in the cell responses at various cell densities provided further evidence for non-thermal mechanism of the observed MW effects.

Significant MW effect on synchronization of *Saccharomyces carlsbergensis* yeast cells were observed by Golant and co-authors (Golant, Kuznetsov et al. 1994). Exposure to MW at 30 $\mu W/cm^2$ and 46 GHz induced synchronization as measured by cell density and bud formation. The authors assumed that MW induced cell-to-cell interaction resulting in the observed synchronization.

Possible role of intrinsic electromagnetic fields in cell-to-cell communication and mechanisms of their generation have recently been reviewed (Cifra, Fields et al. 2011).

XIII. GENETIC BACKGROUND AND CELL TYPE

Belyaev et al. have studied effects of MW on *E. coli* cells of three isogenic strains with different length of chromosomal DNA (Belyaev, Alipov et al. 1993). Bacterial chromosomal DNA in the cells of N99 wild type stain was lengthened by inserting DNA from λ and λ*imm*^{434}*bio*^{10} phages. Two strains were obtained with increased length of chromosomal DNA, N99(λ) and N99(λ,λ*imm*^{434}*bio*^{10}). The cells of these 3 strains were exposed to MW 10^{-10} at W/cm^2 and 10-17 frequencies within the ranges of 41.24-41.37 GHz and 51.69-51.795 GHz. The changes in chromatin conformation were analyzed before and after exposure. Clear resonance responses to MW were observed for each strain in both frequency ranges. However, each strain had its own resonance frequency, which were statistically significantly different between strains. All resonances had the same amplitude and half-width (Belyaev, Alipov et al. 1993). In each frequency band, all 3 resonances had the same effective circular polarization: right-handed in the 41.24-41.37 GHz band and left-handed within 51.69-51.795 GHz. All these data have led to conclusion that lengthening of chromosomal DNA resulted in shifting the resonance MW spectra of action. Importantly, these shifts in resonance frequencies could not be explained by the genetic activity of the inserted DNA. On the other hand, theoretical consideration based on oscillations of the DNA-domains regarding a whole nucleoid provided a good correlation between the increasing in the DNA length and the shifts in resonances (Belyaev, Alipov et al. 1993). A detailed analysis of MW effects on the cells of another *E. coli* strain, AB1157, at 10^{-10} W/cm^2 and various frequencies within 51.69-51.795 GHz, revealed the resonance frequency of 51.755$\pm$0.001 GHz (Belyaev, Shcheglov et al. 1996). This value was statistically significantly different from the resonance frequency of 51.765$\pm$0.002 in response of *E. coli* N99 cells to MW in the same frequency range (Belyaev, Shcheglov et al. 1996). It should be noted that both strains, AB1157 and N99, are considered as wild type strains. Nevertheless, these strains are different in their genotypes by several gene markers (Lukashevsky and Belyaev 1990; Belyaev, Alipov et al. 1992). These data provided evidence that cells of different origin, even being considered as wild type cells, might have different resonance responses to NT MW because of differences in their genotypes.

Stagg with colleagues exposed tissue cultures of transformed and normal rat glial cells to modulated MW (TDMA that conforms to the North American digital cellular telephone standard) at 836.55 MHz (Stagg, Thomas et al. 1997). Results from DNA synthesis assays differed for these two cell types. Sham-exposed and MW-exposed cultures of primary rat glial cells showed no significant differences for either log-phase or serum-starved condition. C6 glioma cells exposed to MW at 5.9

μW/g SAR (0.9 mW/cm^2) exhibited small (20-40 %) but significant increases in 38 % of [^{3}H]-thymidine incorporation experiments.

Repacholi with co-authors chronically exposed wild-type mice and E mu-Pim1 transgenic mice, which are moderately predisposed to develop lymphoma spontaneously, to plane-wave pulse-modulated MW at 900 MHz with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms (Repacholi, Basten et al. 1997). Incident power densities were 2.6-13 W/m^2 and SARs were 0.008-4.2 W/kg, averaging 0.13-1.4 W/kg. The lymphoma risk was found to be significantly higher in the exposed transgenic mice. No effects were seen in the wild type mice.

Markkanen with colleagues found that MW affected the UV-induced apoptosis in *Saccharomyces cerevisiae* yeast cells KFy437 (cdc48-mutant) but did not modify apoptosis in KFy417 (wild-type) cells (Markkanen, Penttinen et al. 2004).

Czyz with colleagues exposed pluripotent embryonic stem (ES) cells of wild-type and deficient for the tumor suppressor p53 to pulse modulated GSM MW at 1.71 GHz (Czyz, Guan et al. 2004). Two dominant GSM modulation schemes (GSM-217 and GSM-Talk), which generate temporal changes between GSM-Basic (active during talking phases) and GSM-DTX (discontinuous transmission, which is active during listening phases thus simulating a typical conversation), were applied to the cells at and below the ICNIRP safety standards, 2 and 1.5 W/kg . GSM-217 MW induced a significant upregulation of mRNA levels of the heat shock protein hsp70 of p53-deficient ES cells differentiating in vitro, paralleled by a low and transient increase of c-jun, c-myc, and p21 levels in p53-deficient, but not in wild-type cells. Theses data further substantiated the notion that the genetic background determines cellular responses to GSM MW.

Nylund and Leszczynski have examined cell response to MW (900 MHz GSM-like signal, average SAR of 2.8 W/kg) using two human endothelial cell lines: EA.hy926 and EA.hy926v1 (Nylund and Leszczynski 2006). Gene expression changes were examined using cDNA Expression Arrays and protein expression changes were examined using 2-DE and PDQuest software. The same genes and proteins were differently affected by exposure in each of the cell lines.

Remondini et al. analyzed changes in gene expression in six human cell lines by gene microarrays (Remondini, Nylund et al. 2006). Cells were exposed to MW at 900 MHz GSM Basic mode, SAR 1.8-2.5 W/kg, 1 h exposure. Most cell lines responded to GSM-900 MHz, except for the CHME5 human microglial cells.

Rat1 and HeLa human cells were subjected to RF exposure at a frequency of 875 MHz with an intensity of 0.07 mW/cm2 (Friedman, Kraus et al. 2007). In Rat1 cells, phosphorylation peaked at 15 min after irradiation and returned to basal level within 30 min, whereas, in HeLa cells, peak phosphorylation was at 5 min after stimulation and decreased thereafter. Increases in Hb-

EGF release upon mobile phone irradiation were detected in both Rat1 and HeLa cell lines, although the amount released from irradiated HeLa cells was much higher than that released from Rat1 cells.

Zhao et al. studied whether expression of genes related to cell death pathways are dysregulated in primary cultured neurons and astrocytes by exposure to MW from GSM cell phone at the frequency of 1900 MHz for 2 h (Zhao, Zou et al. 2007). Microarray analysis and real-time RT-PCR have shown up-regulation of caspase-2, caspase-6 and Asc (apoptosis associated speck-like protein containing a card) gene expression in neurons and astrocytes. Up-regulation occurred in both "on" and "stand-by" modes in neurons, but only in "on" mode in astrocytes. Additionally, astrocytes showed up-regulation of the Bax gene. The authors concluded that even relatively short-term exposure to the cell phone radiation can up-regulate elements of apoptotic pathways in cells derived from the brain, and that neurons appear to be more sensitive to this effect than astrocytes.

Hoyto et al. analyzed the effects of MW exposure on cellular ornithine decarboxylase (ODC) activity in fibroblasts, two neural cell lines and primary astrocytes (Hoyto, Juutilainen et al. 2007). Several exposure times and exposure levels were used, and the fields were either unmodulated or GSM-like-modulated. Murine L929 fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells, and rat primary astrocytes were exposed to RF radiation at 872 MHz in a waveguide exposure chamber equipped with water cooling. Cells were exposed for 2, 8, or 24 hours to CW MW or to a GSM type signal pulse modulated at 217 Hz. ODC activity in rat primary astrocytes was decreased statistically significantly and consistently in all experiments performed at two exposure levels (1.5 and 6.0 W/kg) and using GSM modulated or CW radiation. In the secondary cell lines, ODC activity was generally not affected. The authors concluded that ODC activity was affected by MW exposure in rat primary neural cells, but the secondary cells used in this study showed essentially no response. In further studies by the same group, the difference in response of human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells to a GSM-modulated MW at 872 MHz was replicated (Hoyto, Luukkonen et al. 2008).

Human cultured fibroblasts of three different donors and three different short-term human lymphocyte cultures were exposed to UMTS-like MW at 1950 MHz and the SAR below safety limit of 2 W/kg by Schwarz et al. (Schwarz, Kratochvil et al. 2008). The alkaline comet assay and the micronucleus assay were used to analyze genotoxic effects. UMTS exposure increased the comet tail factor (CTF) and induced centromere-negative micronuclei in human cultured fibroblasts in a dose and time-dependent way. No UMTS effect was obtained with lymphocytes, either unstimulated or stimulated with phytohemagglutinin. The authors concluded that UMTS exposure may cause genetic alterations in some but not in all human cells in vitro.

Del Vecchio et al. have tested viability, proliferation, and vulnerability of neural cells, after continuous radiofrequency (RF) electromagnetic fields exposure (global system for mobile telecommunications (GSM) modulated 900 MHz signal at a specific absorption rate (SAR) of 1 W/kg and maximum duration 144 h) generated by transverse electromagnetic cells. Two cellular systems, SN56 cholinergic cell line and rat primary cortical neurons were used (Del Vecchio, Giuliani et al. 2009). Exposure to RF did not change viability/proliferation rate of the SN56 cholinergic cells or viability of cortical neurons. Co-exposure to RF exacerbated neurotoxic effect of hydrogen peroxide in SN56, but not in primary cortical neurons, whereas no cooperative effects of RF with glutamate and 25-35AA beta-amyloid were found. These data suggest that only under particular circumstances (cell type and type of co-exposure) exposure to GSM modulated, 900MHz signal act as a co-stressor for oxidative damage of neural cells.

Gerner et al. exposed four different human cell types exposed to modulated GSM 1800 MHz at 2 W/kg (Gerner, Haudek et al. 2010). While short-term exposure did not significantly alter the proteome, an 8-h exposure caused a significant increase in protein synthesis in Jurkat T-cells and human fibroblasts, and to a lesser extent in activated primary human mononuclear cells (Gerner, Haudek et al. 2010). Quiescent (metabolically inactive) mononuclear white blood cells, did not detectably respond to GSM 1800 MHz. Most of the proteins found to be induced were chaperones, which are mediators of protein folding. Heat-induced proteome alterations detectable with used proteome methodology would require heating greater than 1°C. Because GSM-induced heating was less than 0.15°C, a heat-related response was excluded.

Dragicevic et al. evaluated brain mitochondrial function in aged Tg mice and non-transgenic (NT) littermates following 1 month of daily exposure to EMF at 918 MHz frequency, involved modulation with Gaussian minimal-shift keying (GMSK) signal, and SAR levels that varied between 0.25 and 1.05 W/kg (Dragicevic, Bradshaw et al. 2011).The cognitively-important brain areas of cerebral cortex and hippocampus in EMF-exposed mice exhibited clear increases in maximum mitochondrial respiration, while the striatum and amgydala were unaffected. For Tg mice, long-term EMF treatment induced a dramatic reduction in mitochondrial ROS levels in both cerebral cortex and hippocampus, but not in striatum or amygdala. By contrast, NT mice given EMF treatment did not show significant changes in ROS levels within any of the four brain areas analyzed. Therefore, EMF treatment reduced ROS levels selectively in Tg mice and selectively in cognitively-important brain areas.

Finally, it follows from the emerging data that MW effects are dependent on genotype and cell-type. These dependences may explain, at least partly, the discrepancies among studies from

different laboratories and demand careful selection of biological objects in designing the replication studies.

XIV. SEX-AND AGE-RELATED DIFFERENCES

There are few studies consistently indicating that MW may exert a sex-related influence on brain activity.

Papageorgiou and co-authors investigated the sex-related influence of MW similar to that emitted by GSM900 mobile phones on brain activity (Papageorgiou, Nanou et al. 2004). Baseline EEG energy of males was greater than that of females, and exposure to MW decreased EEG energy of males and increased that of females. Memory performance was invariant to MW exposure and sex influences.

Smythe and Costall reported the effects of mobile phone exposure on short- and long-term memory in male and female subjects (Smythe and Costall 2003). The results showed that males exposed to an active phone made fewer spatial errors than those exposed to an inactive phone condition, while females were largely unaffected. These results further indicated that mobile phone exposure has functional consequences for human subjects, and these effects appear to be sex-dependent.

Nam and colleagues exposed volunteers of both sex to MW emitted by a CDMA cellular phone for half an hour (Nam, Kim et al. 2006). Physiological parameters such as systolic and diastolic blood pressures, heart rate, respiration rate, and skin resistance were simultaneously measured. All the parameters for both groups were unaffected during the exposure except for decreased skin resistance of the male subjects (Nam, Kim et al. 2006).

Güler et al. exposed infant female and male white rabbits to 1800 MHz GSM like RF signal at SAR of 1.8 W/kg for 15 min/day during 7-14 days (Guler, Tomruk et al. 2012). Lipid peroxidation levels in the liver tissues of female and male infant rabbits increased under RF radiation exposure. Liver 8-hydroxy-2 ’-deoxyguanosine (8-OHdG) levels of female rabbits exposed to RF radiation were also found to increase when compared with the levels of non-exposed infants. However, there were no changes in liver 8-OHdG levels of male rabbits under RF exposure.

Santini et al. have performed a survey study on symptoms experienced during use of digital cellular phones using questionnaire of 161 students and workers in a French engineering school (Santini, Seigne et al. 2001). A significant increase in concentration difficult ($p < 0.05$) was reported by users of 1800-MHz (DCS) cellular phones compared to 900-MHz (GSM) phone users.

In users of cellular phones, women significantly ($p < 0.05$) complained more often of sleep disturbance than men. This sex difference for sleep complaint was not observed between women and men non-users of cellular phone. The use of both cellular phones and VDT significantly increased concentration difficulty. Digital cellular phone users also significantly ($p < 0.05$) more often complained of discomfort, warmth, and picking on the ear during phone conversation in relation with calling duration per day and number of calls per day. The complaint warmth on the ear might be a signal to users for stopping the call.

Prevalence of women (usually around 70%) among subjects, which report hypersensitivity to electromagnetic fields of wide frequency range including MW, may also provide indirect evidence for the gender-dependent effects of MW.

In his pioneering study concerning age in cancer risk from MW exposure, Hardell and colleagues found that the highest risks were associated with >5-year latency period in the youngest age group studied, 20-29-year, for analog phones (OR = 8.17, 95% CI = 0.94-71), and cordless phones (OR = 4.30, 95% CI = 1.22-15) (Hardell, Mild et al. 2004). Of note, no participants of age less 20 years were involved on this study. In further studies from the Hardell's group, highest risk was found in the age group <20 years at time of first use of wireless phones (Hardell and Carlberg 2009; Hardell, Carlberg et al. 2009).

Nam with co-authors reported that skin resistance in teenagers decreased by exposure to CDMA MW from cellular phones whereas no effects were seen in adults (Nam, Kim et al. 2006).

Capri et al. analyzed CD25, CD95, CD28 molecules in unstimulated and stimulated CD4+ e CD8+ T cells in vitro (Capri, Salvioli et al. 2006). Peripheral blood mononuclear cells (PBMCs) from young and elderly donors were exposed or sham-exposed to RF (1,800 MHz, SAR 2 W/kg) with or without mitogenic stimulation. No significant changes in the percentage of these cell subsets were found between exposed and sham-exposed lymphocytes in both young and elderly donors. Nevertheless, RF exposure induced a slight, but significant, downregulation of CD95 expression in stimulated CD4+ T lymphocytes from elderly, but not from young donors. This age-related result is noteworthy given the importance of such molecule in regulation of the immune response.

XV. INDIVIDUAL TRAITS

Shckorbatov et al. investigated electrokinetic properties of cell nuclei and condensation of heterochromatin in human buccal epithelium cells in response to MW at 42.2 GHz (Shckorbatov,

Grigoryeva et al. 1998). MW exposure decreased electric charge of cell nuclei and an increased chromatin condensation in dependence on individual traits of donors.

Individual variability in effects of GSM and UMTS MW on chromatin conformation and 53BP1/γ-H2AX DNA repair foci was observed in studies with lymphocytes from hypersensitive to EMF subjects and healthy persons (Sarimov, Malmgren et al. 2004; Belyaev, Hillert et al. 2005; Markova, Hillert et al. 2005; Belyaev, Markova et al. 2009). The same individual variability was reported for response of chromatin condensation human lymphocytes to ELF magnetic fields (Sarimov, Alipov et al. 2011). This variability correlated with initial state of chromatin in the exposed cells (Sarimov, Alipov et al. 2011). Thus, the data from two different research groups have indicated that the NT MW effects on human cells depended on initial sate of chromatin that individually varied between subjects.

Zotti-Martelli with colleagues exposed peripheral blood lymphocytes from nine different healthy donors for 60, 120 and 180 min to CW MW with a frequency of 1800 MHz and PD of 5, 10, and 20 mW/cm^2 and analyzed DNA damage using micronucleus (MN) assay (Zotti-Martelli, Peccatori et al. 2005). Both spontaneous and induced MN frequencies varied in a highly significant way among donors, and a statistically significant increase of MN, although rather low, was observed dependent on exposure time and PD. The data analysis highlighted a wide inter-individual and reproducible variability in the response.

Hinrikus et al. (Hinrikus, Bachmann et al. 2008) evaluated the effects of pulse-modulated MW (450 MHz) on human EEG rhythms. Thirteen healthy volunteers were exposed to MW; the field power density at the scalp was 0.16 m W/cm^2. Differences were found in individual sensitivity to exposure. Increases in the EEG beta power appeared statistically significant in the case of four subjects. In other study, the same authors confirmed and extended their observations on individual sensitivity to exposure with pulse-modulated MW. The experiments were carried out on four different groups of healthy volunteers. A 450-MHz MW modulated at 7 Hz (first group), 14 and 21 Hz (second group), 40 and 70 Hz (third group), 217 and 1000 Hz (fourth group) frequencies was applied. MW exposure, SAR 0.303 W/kg, increased the EEG energy. The proportion of subjects significantly affected was similar in all groups except for the 1000 Hz group: in the first group 16% at 7 Hz modulation; in the second group 31% at 14 Hz modulation and 23% at 21 Hz modulation; in the third group 20% at 40 Hz and 13% at 70 Hz modulation; in the fourth group 16% at 217 Hz and 0% at 1000 Hz modulation frequency.

Sannino et al. evaluated the induction of micronuclei in response to MW (900 MHz, average SAR of 1.25 W/kg) exposure and subsequent treatment with mitomycin C in peripheral blood lymphocytes from five human volunteers (Sannino, Sarti et al. 2009). MW exposure reduced the

level of mitomycin C –induced micronuclei in cells collected from four donors (i.e., responders). However, the effect of MW was not observed in the remaining donor (i.e., non-responder). The overall data indicated the existence of heterogeneity in the MW response among individuals.

Human sensitivity to radio frequency (RF) standing waves was tested using a movable reflecting wall (Huttunen, Hanninen et al. 2009). When the reflector was moved, the position of the maximums of the standing waves changed and the electromagnetic intensity changed in the body of the standing test subject. The computer with an AD-converter registered the signals of the hand movement transducer and the RF-meter with 100MHz dipole antennas. A total of 29 adults of different ages were tested. There were 9 persons whose hand movement graphs included features like the RF-meter. Six showed responses that did not correlate with the RF-meter. There were also 14 persons who did not react at all. Sensitive persons seem to react to crossing standing waves of the RF signals.

To conclude, while only few studies were performed, to evaluate individual sensitivity, the obtained results indicate dependence of response to MW exposure on individual traits.

XVI. PHYSIOLOGICAL VARIABLES: STAGE OF CELL GROWTH, TEMPERATURE, OXYGEN, DIVALENT METALS

The importance of physiological variables, which may include all conditions of cell culture growth such as aeration, the composition of the growth and exposure media, on NT MW effects has previously been reviewed (Grundler, Jentzsch et al. 1988). Since that time, significant body of new data has been accumulated unequivocally supporting the role of physiological variables for the NT MW effects, which should be carefully taken into account when replicating the original studies.

Belyaev et al. have reported that both value and direction of the MW effects strongly depended on the phase of culture growth, at which *E. coli* cells were exposed to CP or LP MW (100 $\mu W/cm^2$) at the resonance frequencies of 41.32 GHz and 51.76 GHz (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994). At logarithmic phase of growth, MW resulted in condensation of nucleoids. In contrast, MW exposure decondensed nucleoids in cells if exposure was performed at the stationary phase of growth. It is known, that the state of nucleoid condensation depends on cell activity. In stationary cells nucleoids are more condensed compared to logarithmic cells that divide actively. It was concluded that MW are able to either stimulate or inhibit activity of the cells in dependence on stage of growth, stationary or logarithmic, respectively. Higher variability in effects was observed for logarithmic phase and effects were more stable for the stationary phase

that is characterized by partial synchronization of cells (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994). There was no effect at all if cells were exposed at the end of the logarithmic phase where the MW effects changed their direction from inhibition to stimulation (Belyaev, Alipov et al. 1994). Another peculiarity was observed at the very beginning of the logarithmic stage, where the condensation of chromatin induced by MW was relatively weak. The AVTD data were confirmed by the electrophoretic analysis of proteins bound to DNA (Belyaev, Shcheglov et al. 1993). The effect in the stationary phase was characterized by a decrease in the quantity of several DNA-bound proteins with molecular weights of 61, 59, 56, 26, and 15 kDa. In contrast, abundance of some DNA-bound proteins, 61, 56, 51 and 43 kDa increased after exposure at the logarithmic phase. The decrease or increase in the abundance of DNA-bound proteins correlated with the observed changes in the state of nucleoids, decondensation or condensation, respectively.

Shcheglov et al. have studied effects of MW at the PD range of 10^{-18} to $3 \cdot 10^{-3}$ W/cm^2 stationary on logarithmic and stationary cells at various cell densities (Shcheglov, Alipov et al. 2002). Relatively weak response to MW was observed in exponentially growing cells. Partially synchronized stationary cells were more sensitive, especially at the cell densities above 10^8 cell/ml. The data suggested that the co-operative responses of cells to MW vary in dependence on phase of growth.

Recent data by Ushakov and colleagues indicated that the MW effects on *E. coli* cells depended on concentration of oxygen in the cell suspension during exposure (Ushakov, Alipov et al. 2005). This dependence might suggest that oxygen concentration should be indicated in order to improve reproducibility in replication studies.

Biological systems have been shown to be very sensitive to perturbations at conditions where critical components are at phase transition points, governed by local temperature, ionic strength and pH. This phenomenon was demonstrated by independent laboratories using 2.45-GHz MW radiation associated with a phase transition in lipid-protein complexes around 20-25 ^{0}C (Olcerst, Belman et al. 1980; Fisher, Poznansky et al. 1982; Liburdy and Vanek 1985; Allis and Sinha-Robinson 1987; Liburdy and Vanek 1987).

Fisher et al. have reported an effect of low-level 2450-MHz MW on total and ouabain-sensitive $24Na^+$ flux from human erythrocytes. Erythrocytes washed and loaded with $24Na^+$ were exposed at an absorption rate of 2.0-3.0 mW/ml suspension in a waveguide system under temperature- controlled conditions for 1 or 2 hr. Experiments were run in parallel, with exposed and sham- irradiated (control) samples, at various temperatures between 7 and 35^{0}C. Continuous-wave electromagnetic radiation at 2450 MHz had a significant effect on $24Na^+$ efflux, but only in the temperature range 22-25^{0}C. Total efflux increased an average of 23%; this was the result of an

increase in the ouabain-insensitive component (mean, 33%) and a decrease in the ouabain- sensitive portion (mean, 18%). These results indicated increased passive Na+ efflux and decreased ATPase-mediated Na+ efflux in erythrocytes exposed to low-level microwaves at 22-25^{0}C (Fisher, Poznansky et al. 1982).

Liburdy and Vanek have shown that MW-induced protein shedding is oxygen and temperature dependent (Liburdy and Vanek 1987). Microwaves (2450 MHz, 60 mW/g) resulted in the release or shedding of at least 11 low-molecular-weight proteins (<31,000 Da) from rabbit erythrocytes maintained in physiological buffer. This release was oxygen dependent and occured in 30 min for exposures conducted within the special temperature region of 17-21^{0}C, which is linked to a structural or conformational transition in the cell membrane. Shedding of 26,000 and 24,000 Da proteins was unique to MW treatment, with enhanced release of 28,000 and < 15,000 Da species upon MW exposure. Two-dimensional isoelectric focusing revealed that proteins of< 14,000 Da shed during microwave treatment exhibited a pI of 6.8-7.3 not seen in sham-treated cells. When erythrocytes were maintained at 17-21^{0}C in the absence of divalent cations, release of 28,000-31,000 and < 14,000 Da components was detected. This indicated that cation-bridge stability may be important for release of these proteins. The results provided evidence that MW alter erythrocyte protein composition at temperatures linked to a transition in the cell membrane and that destabilization of salt bridges may play a role in an interaction mechanism for protein release (Liburdy and Vanek 1987).

The ATPase activity in human red blood cell membranes was investigated in vitro as a function of temperature and exposure to 2,450-MHz continuous wave microwave radiation to confirm and extend a report of Na^+ transport inhibition under certain conditions of temperature and exposure (Allis and Sinha-Robinson 1987). Assays were conducted spectrophotometrically during microwave exposure with a custom-made spectrophotometer-waveguide apparatus. Temperature profiles of total ATPase and Ca^{+2} ATPase (ouabain-inhibited) activity between 17 and 31 degrees C were graphed as an Arrhenius plot. Each data set was fitted to two straight lines which intersect between 23 and 24 degrees C. The difference between the total and Ca^{+2} ATPase activities, which represented the Na^+/K^+ ATPase activity, was also plotted and treated similarly to yield an intersection near 25 degrees C. Exposure of membrane suspensions to electromagnetic radiation, at a dose rate of 6 W/kg and at five temperatures between 23 and 27 degrees C, resulted in an activity change only for the Na^+/K^+ ATPase at 25 degrees C. The activity decreased by approximately 35% compared to sham-irradiated samples. A possible explanation for the unusual temperature/microwave interaction was proposed (Allis and Sinha-Robinson 1987).

Therefore, temperature may be an important variable, which should be taken into account while analyzing response of cells to MW.

Similar to the effects of ELF (Belyaev, Alipov et al. 1999), the MW effects were reported to be dependent on concentration of divalent ions (Gapeev, Iakushina et al. 1997).

In conclusion, physiological parameters such as stage of cell growth, temperature, oxygen an divalent ions temperature may be an important variable, which should be taken into account while analyzing response of cells to MW.

XVII. ANTIOXIDANTS AND RADICAL SCAVENGERS

Oxidative stress caused by biological, chemical and physical factors has been associated with increased risk of human cancer at various sites. Human cells induce and/or activate several oxidant generating enzymes that produce high concentrations of diverse free radicals and oxidants. These reactive species can damage DNA, RNA, lipids and proteins, leading to increased mutations and altered function of enzymes and proteins, thus contributing to the multistage carcinogenesis process. Control of oxidative stress is being explored as an approach to chemoprevention of human cancers (IARC 2002).

It is well known that endogenous (intracellular) free radicals, which are collectively called reactive oxygen species (ROS), arise from mitochondrial oxidative metabolism and other reactions in cells (Pollycove and Feinendegen 2003). The estimated average generation rate is $\sim 10^9$ ROS per cell per day (Beckman and Ames 1998), which results in 10^6 oxidative DNA damage, 10^5 SSBs and 0.1 DSBs per cell per day (Pollycove and Feinendegen 2003).

In their pioneering study, Lai and Singh described the effects of MW on the rat brain cells as measured using a microgel electrophoresis assay (Lai and Singh 1996). These effects were significantly blocked by treatment of rats either with the spin-trap compound N-tert-butyl-α-phenylnitrone or with melatonin, both agents being free radical scavengers and antioxidants (Lai and Singh 1997). These data suggested that free radicals might be involved in the effects of MW. The ability of scavengers and antioxidants has been tested by many other research groups an in all cases, this treatment inhibiter the reported TN MW effects.

Oktem andcolleagues exposed rats to MW from GSM900 mobile phone with and without melatonin treatment (Oktem, Ozguner et al. 2005). Malondialdehyde (MDA), an index of lipid peroxidation, and urine N-acetyl-beta-d-glucosaminidase (NAG), a marker of renal tubular damage, were used as markers of oxidative stress-induced renal impairment. Superoxide dismutase (SOD),

catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate changes in antioxidant status. In the MW-exposed group, while tissue MDA and urine NAG levels increased, SOD, CAT, and GSH-Px activities were reduced. Melatonin treatment inhibited these effects. The authors concluded that melatonin might exhibit a protective effect on mobile phone-induced renal impairment in rats.

Ozguner and colleagues exposed Wistar-Albino rats to MW from GSM900 mobile phone with and without melatonin and analyzed histopathologic changes in skin (Ozguner, Aydin et al. 2004). MW induced increase in thickness of stratum corneum, atrophy of epidermis, papillamatosis, basal cell proliferation, granular cell layer (hypergranulosis) in epidermis and capillary proliferation. Impairment in collagen tissue distribution and separation of collagen bundles in dermis were all observed in exposed animals as compared to the control group. Most of these changes, except hypergranulosis, were prevented with melatonin treatment. The authors concluded that exposure to GSM900 MW caused mild skin changes and melatonin treatment could reduce these changes. In other studies of the same group, the ability of melatonin to reduce various MW-induced effects was confirmed and inhibitory potential of the antioxidant caffeic acid phenethyl ester (CAPE) was reported (Ozguner, Altinbas et al. 2005; Ozguner, Oktem et al. 2005; Ozguner, Oktem et al. 2005; Ozguner, Bardak et al. 2006).

Ayata et al. analyzed the effects of 900 MHz MW with and without melatonin on fibrosis, lipid peroxidation, and anti-oxidant enzymes in rat skin (Ayata, Mollaoglu et al. 2004). The levels of MDA and hydroxypyroline and the activities of SOD, GSH-Px, and CAT were studied. MDA and hydroxyproline levels and activities of CAT and GSH-Px were increased significantly in the exposed group without melatonin and decreased significantly in the exposed group with melatonin. SOD activity was decreased significantly in the exposed group and this decrease was not prevented by the melatonin treatment. The authors assumed that the rats irradiated with MW suffer from increased fibrosis and lipid peroxidation and that melatonin can reduce the fibrosis and lipid peroxidation caused by MW.

Ilhan with co-authors investigated oxidative damage in brain tissue of rats exposed to GSM900 MW with and without pretreatment with Ginkgo biloba (Gb) (Ilhan, Gurel et al. 2004). MW induced oxidative damage measured as: (i) increase in MDA and nitric oxide (NO) levels in brain tissue, (ii) decrease in brain SOD and GSH-Px activities, and (iii) increase in brain xanthine oxidase and adenosine deaminase activities. These MW effects were prevented by the Gb treatment. Furthermore, Gb prevented the MW-induced cellular injury in brain tissue revealed histopathologically. The authors concluded that reactive oxygen species may play a role in the

adverse effects of GSM900 MW and Gb prevents the MW-induced oxidative stress by affecting antioxidant enzymes activity in brain tissue.

Guney et al.examined 900 MHz mobile phone-induced oxidative stress that promotes production of ROS and investigated the role of vitamins E and C, which have antioxidant properties, on endometrial tissue against possible 900 MHz mobile phone-induced endometrial impairment in rats (Guney, Ozguner et al. 2007). The animals were randomly grouped (eight each) as follows: 1) Control group (without stress and EMR, Group I), 2) sham-operated rats stayed without exposure to EMR (exposure device off, Group II), 3) rats exposed to 900 MHz EMR (EMR group, Group III) and 4) a 900 MHz EMR exposed + vitamin-treated group (EMR + Vit group, Group IV). A 900 MHz EMR was applied to EMR and EMR + Vit group 30 min/day, for 30 days. Endometrial levels of nitric oxide (NO, an oxidant product) and malondialdehyde (MDA, an index of lipid peroxidation), increased in EMR exposed rats while the combined vitamins E and C caused a significant reduction in the levels of NO and MDA. Likewise, endometrial superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) activities decreased in EMR exposed animals while vitamins E and C caused a significant increase in the activities of these antioxidant enzymes. In the EMR group histopathologic changes in endometrium, diffuse and severe apoptosis was present in the endometrial surface epithelial and glandular cells and the stromal cells. Diffuse eosinophilic leucocyte and lymphocyte infiltration were observed in the endometrial stroma whereas the combination of vitamins E and C caused a significant decrease in these effects of EMR. It is concluded that oxidative endometrial damage plays an important role in the 900 MHz mobile phone-induced endometrial impairment and the modulation of oxidative stress with vitamins E and C reduces the 900 MHz mobile phone-induced endometrial damage both at biochemical and histological levels.

Koylu et al. studied the effects of MW on the brain lipid peroxidation in rats, and the possible protective effects of melatonin on brain degeneration induced by MW (Koylu, Mollaoglu et al. 2006). The levels of lipid peroxidation in the brain cortex and hippocampus increased in the MW group compared with the control group, although the levels in the hippocampus were decreased by combined administration of MW and melatonin. Brain cortex lipid peroxidation levels were unaffected by melatonin treatment. The authors concluded that melatonin may prevent MW-induced oxidative stress in the hippocampus by strengthening the antioxidant defense system.

Balci et all exposed albino Wistar rats to mobile-phone-emitted radiation and analyzed oxidant/antioxidant balance in corneal and lens tissues. The results of this study suggest that mobile telephone radiation leads to oxidative stress in corneal and lens tissues and that antioxidants such as vitamin C can help to prevent these effects (Balci, Devrim et al. 2007).

Sokolovic et al. evaluated the intensity of oxidative stress in the brain of Wistar rats chronically exposed to MW from mobile phones (SAR = 0.043-0.135 W/kg) during 20, 40 and 60 days (Sokolovic, Djindjic et al. 2008). A significant increase in brain tissue malondialdehyde (MDA) and carbonyl group concentration was found. Decreased activity of catalase (CAT) and increased activity of xanthine oxidase (XO) remained after 40 and 60 days of MW exposure. Melatonin treatment significantly prevented the increases in MDA content and XO activity in the brain tissue after 40 days of exposure while it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents. The authors concluded that exposure to the mobile phone MW caused oxidative damage in the brain and that treatment with melatonin significantly prevented this oxidative damage.

Gajski and Garaj-Vrhovac investigated the radioprotective effect of bee venom against DNA damage induced by 915-MHz microwave radiation (SAR of 0.6 W/kg) (Gajski and Garaj-Vrhovac 2009). Whole blood lymphocytes of Wistar rats are treated with 1 mg/mL bee venom 4 hours prior to and immediately before irradiation. Standard and formamidopyrimidine-DNA glycosylase (Fpg)–modified comet assays were used to assess basal and oxidative DNA damage produced by ROS. Bee venom decreased basal and oxidative DNA damage induced by microwave radiation. The difference between the comet assay results in the presence and in the absence of Fpg-enzyme suggested that oxidative stress is responsible for the DNA damage induced by microwave radiation. Among other possible mechanisms, antioxidant activity of bee venom may likely account for the radioporotective effect.

Esmekaya et al. analyzed effects of 1.8 GHz GSM alone and in combination with Ginkgo biloba (EGb 761) pre-treatment in human peripheral blood lymphocytes (Esmekaya, Aytekin et al. 2011). RF exposure significantly increased frequency of sister chromatid exchanges (SCE) and inhibited cell viability. No temperature difference was observed between sham control and RF exposed cells, so the observed effects may be considered as non-thermal. EGb 761 pre-treatment significantly reduced both RF effects. The authors concluded that EGb 761 had a protective role against RF induced mutagenesis.

Ozgur et al investigated oxidative damage and antioxidant enzyme status in the liver of guinea pigs exposed to mobile phone-like radiofrequency radiation (RFR) and the potential protective effects of N-acetyl cysteine (NAC) and epigallocatechin-gallate (EGCG) on the oxidative damage (Ozgur, Gler et al. 2010). Nine groups of guinea pigs were used to study the effects of exposure to an 1800-MHz Global System for Mobile Communications (GSM)-modulated signal (average whole body Specific Absorption Rate (SAR) of 0.38W/kg, 10 or 20 min per day for seven days) and treatment with antioxidants. Significant increases in malondialdehyde (MDA) and total

nitric oxide (NO) levels and decreases in activities of superoxide dismutase (SOD), myeloperoxidase (MPO) and glutathione peroxidase (GSH-Px) were observed in the liver of guinea pigs after RFR exposure. NAC treatment induced increase in hepatic GSH-Px activities, whereas EGCG treatment alone attenuated MDA level. Extent of oxidative damage was found to be proportional to the duration of exposure. Authors concluded that the adverse effect of RFR may be related to the duration of mobile phone use. NAC and EGCG may protect the liver tissue against the RFR-induced oxidative damage and enhance antioxidant enzyme activities.

Female rats were exposed to a mobile phone signal (900 MHz), the mobile phone plus vitamin C group was exposed to a mobile phone signal (900 MHz) and treated orally with vitamin C (Imge, Kilicoglu et al. 2010). Malondialdehyde (MDA), antioxidant potential (AOP), superoxide dismutase, catalase (CAT), glutathione peroxidase (GSH-Px), xanthine oxidase, adenosine deaminase (ADA) and 5'nucleotidase (5'-NT) were analyzed in brain tissues. MW exposure caused an inhibition in 5'-NT and CAT activities. GSH-Px activity and the MDA level were also found to be reduced in the mobile phone group but not significantly. Vitamin C caused a significant increase in the activity of GSH-Px and non-significant increase in the activities of 5'-NT, ADA and CAT enzymes. The results suggest that vitamin C may play a protective role against detrimental effects of mobile phone radiation in brain tissue.

To conclude this section, several studies consistently show that supplementation with antioxidants and radical scavengers can reduce MW effects. In other words, the level of radicals should be considered as an important parameter for the NT MW effects. Moreover, these studies indicate that induction of radicals is one of the key events in bioeffeds of NT MW.

XVIII. CO-EXPOSURE

Zmyslony et al have studied effects of 930 MHz continuous wave (CW) electromagnetic field, 1.5 W/kg, on the reactive oxygen species (ROS) level in rat lymphocytes (Zmyslony, Politanski et al. 2004). Acute (5 and 15 min) exposure did not induce ROS. However, this exposure increased effect of $FeCl_2$, 10 μg/ml.

Co-exposure to RF (global system for mobile telecommunications (GSM) modulated 900MHz signal at a specific absorption rate (SAR) of 1 W/kg and maximum duration 144 h) exacerbated neurotoxic effect of hydrogen peroxide in SN56, but not in primary cortical neurons (Del Vecchio, Giuliani et al. 2009). These data suggest that only under particular circumstances

(cell type and type of co-exposure) exposure to GSM modulated, 900MHz signal act as a co-stressor for oxidative damage of neural cells.

XIX. REPLICATION STUDIES

Obviously, not taking into account the dependences of NT MW effects on a number of physical parameters and biological variables may result in misleading conclusions regarding the reproducibility of these effects. Especially important might be the observations that NT MW could inhibit or stimulate the same functions dependent on conditions of exposure (Pakhomov, Akyel et al. 1998). Under different conditions of exposure, MW either increased or decreased the growth rate of yeast cells (Grundler, Jentzsch et al. 1988), the radiation-induced damages in mice (Sevast'yanova 1981), the respiratory burst in neutrophils of mice (Gapeev, Iakushina et al. 1997), the condensation of nucleoids in *E coli* cells (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994) and human lymphocytes (Sarimov, Malmgren et al. 2004). Potentially bi-directional effects of MW should be taken into account in replication studies.

In some cases when the conditions were kept in strict control, the effects we reproduced. Highly resonant effects of ultra-weak MW (near 70 GHz) on the induction of λ-phage were first established by Webb (Webb 1979), and subsequently corroborated (Lukashevsky and Belyaev 1990).

Despite of considerable body of studies with NT MW in biology, only a few studies were performed to independently replicate the original data on the NT MW effects. It should be noted, that these replications are usually not completely 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. One well-known attempt to replicate the results of Gründler was the study by Gos and co-authors (Gos, Eicher et al. 1997). No MW effects were observed in this replication study. However, the deviations from the Gründler's protocol might be a simple reason for poor reproducibility. For example, synchronized cells were used in studies of Gründler. Contrary to the Gründler's original protocol, Gos used exponentially growing cells. If the MW effects in yeast cells are dependent on stage of growth, cell density and intercellular interactions as it has been described for *E. coli* cells (Belyaev, Shcheglov et al. 1993; Belyaev, Alipov et al. 1994; Belyaev, Shcheglov et al. 1996; Shcheglov, Belyaev et al. 1997), no response should be expected in the logarithmic phase of growth. Gos and colleagues used *S. cerevisiae* strain with the auxotrophy mutations for leucine and uracil. Gründler used the wild type strain. It might

suggest another cause for the deviations between the data of Gründler and Gos. Despite orientation of SMF in respect to electric and magnetic components of MW was the same, the values of SMF were different. The stray ELF field was 120 nT in the study by Gos, that is higher than usually observed background fields, < 50 nT. The spectral characteristics of the background fields, which were described only in the study by Gos, might be also different. In addition, the conditions of cell cultivation might vary between studies; for example, the data on oxygen concentration in media used in both studies are not available.

Lai and Singh have consistently reported that circularly polarized MW exposure at 2450 MHz induced DNA damage in brain cells of the exposed rats (Lai and Singh 1995; Lai and Singh 1996; Lai and Singh 1997). Replication studies have also tested circularly polarized MW exposure at 2450 MHz and no induced DNA damage was reported (Malyapa, Ahern et al. 1997; Malyapa, Ahern et al. 1998; Lagroye, Anane et al. 2004). All these replication studies have used another exposure system. However, handedness of circular polarization has not been given neither in original study, no in replications. If the handedness was different between studies it could reasonably account for inconsistency.

Most reviews of the experimental studies do not include analysis of various biological variables and physical parameters when comparing the data on the NT MW effects from different studies. As result, misleading conclusion is often made that MW at NT levels produce no "reproducible" effects.

XX. SIMILARITY OF MICROWAVE AND ELF EFFECTS

Mobile phones not only expose the user to RF EMF but also to ELF EMF (Linde and Mild 1997; Heath, Jenvey et al. 1998; Jokela, Puranen et al. 2004; Ilvonen, Sihvonen et al. 2005; Cook, Saucier et al. 2006; Perentos, Iskra et al. 2007). Perentos et al. have recently measured and characterized the ELF magnetic field from several commercial GSM handsets (the RF characteristics being already well understood) using different probes which covered frequency range from static magnetic fields ("0 Hz") to 2 GHz. Peak ELF fields at the front sides of 5 commercial GSM phones were assessed and a maximum of 22.4 μT was reported (Perentos, Iskra et al. 2008). The main ELF component at the 217 Hz was about 1 μT at the distance of 3 cm from the handset front side. The overall pulse peak was 4.2 times greater than the 217 Hz component. 217 Hz magnetic field decreased with distance and reached 0.3 μT approximately at 5 cm from the front handset side. The overall ELF pulse peak produced by all ELF components was 4.2 times greater

than the 217 Hz component. The ELF fields higher 0.3 μT have consistently been shown to correlate with increased risk of children leukemia in several studies covering European countries, USA and Japan (Kabuto, Nitta et al. 2006; Yang, Jin et al. 2008). Similar to RF, ELF has been classified by the IARC as possible carcinogen "2B". It has been known for long time that weak ELF fields and NT MW result to similar effects with significant overplaying of molecular biological pathways for their appearance (Adey 1981; Blank and Goodman 2009; Davanipour and Sobel 2009). Multiple data on ELF biological effects at intensities below the ICNIRP standards are available showing their complex dependence of the ELF effects on biological and physical variables (Belyaev, Alipov et al. 1999; Blank and Goodman 2009; Phillips, Singh et al. 2009; Sarimov, Alipov et al. 2011). In particular, stress response, molecular pathways for generation of reactive oxygen species (ROS), increased sensitivity of stem cells, and inhibition of melatonin production (Burch, Reif et al. 2000) were suggested as mechanisms which link observed increase in cancer risks and effects of exposure at the cellular level. EMF effects in a wide frequency range from ELF to MW have been considered in the frames of the same physical models (Chiabrera, Bianco et al. 1991; Matronchik, Alipov et al. 1996; Chiabrera, Bianco et al. 2000; Binhi 2002; Panagopoulos, Karabarbounis et al. 2002; Matronchik and Belyaev 2005; Matronchik and Belyaev 2008).

In many cases, because of ELF modulation and additional ELF fields created by the MW sources, for example by mobile phones, it is difficult to distinguish the effects of exposures to ELF and MW. Therefore, these combined exposures and their possible cancer risks should be considered in combination.

XXI. CANCER RISK ASSESSMENT FROM MECHANISTIC POINT OF VIEW

At present, a new situation has arisen when a significant part of the general population is exposed chronically (much longer than previously investigated durations of exposures) to NT MW from different types of mobile communication including GSM and UMTS/3G phones and base stations, WLAN (Wireless Local Area Networks), WPAN (Wireless Personal Area Networks such as Bluetooth), DECT (Digital Enhanced (former European) Cordless Telecommunications) wireless phones (Joseph, Frei et al. 2010). Multiple sources of mobile communication result in chronic exposure of general population to MW at the non-thermal levels. These exposures are characterized by low intensities, varieties and complexities of signals, and long-term durations of exposure that are comparable with a lifespan.

Most of the real signals that are in use in mobile communication have not been tested so far. 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 aspects as intensity, carrier frequency, modulation, polarization, duration and intermittence.

Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, is not useful alone for the evaluation of health risks from NT MW of mobile communication. The role of other exposure parameters such as frequency, modulation, polarization, duration, and intermittence of exposure should be taken into account.

IARC has recently classified RF as a 'Possible Human Carcinogen' (Class 2B) (Baan, Grosse et al. 2011). Contrary to other panels, such as ICNIRP, whose members dismiss the NT MW effects based on their "non-reproducibility" and lack of comprehensive mechanisms, the IARC working group included scientists, which argued for existence of non-thermal effects and their complex dependence on variety of biological and physical parameters which should be included in consideration. By its classification, IARC has justified implementation of the Precautionary Principle, confirmed the existence of non-thermal effects that can cause health risks, and indicated that the current safety standards are insufficient to protect health.

The data about the effects of MW at super low intensities 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, wireless routers, WI-FI and other wireless devices and exposures in common use today can also produce adverse effects at prolonged durations of exposure.

So far, most laboratory and epidemiological studies did not control important features of the NT MW effects and therefore, only limited conclusion regarding health effects of MW from mobile communication can be drawn from these studies. The group of Hardell was the first epidemiologic studying separately the MW signals from cordless phones, analogue phones and digital phones (Hardell, Hansson Mild et al. 2001; Hardell, Hansson Mild et al. 2003; Hardell, Eriksson et al. 2005; Hardell and Hansson Mild 2005). This approach is valid from the mechanistic point of view.

Nowadays, it is almost impossible to select control unexposed groups because the whole population in many countries is exposed to wide range of MW signals from various sources such as mobile phones, base stations/masts, WLAN, WPAN, DECT wireless phones and given that duration of exposure (at least 10 years for cancer latency period) is also important for the effects of NT MW along PD/SAR. Exposure from downlink sources (base stations *etc.*) may contribute up to

90% of total environmental outdoor-urban exposure in European countries while exposure to DECT phone is comparable to exposure to mobile phones (Frei, Mohler et al. 2009; Frei, Mohler et al. 2010; Joseph, Frei et al. 2010). In other words, there are no unexposed control groups available for epidemiologic studies in the developed countries. Substantial variation in relative ratio of downlink and uplink signals between countries (Joseph, Frei et al. 2010) can at least partially account for differences in epidemiologic data because of variation in exposure of control groups to downlink signals.

While several national registers (Norway, Australia, Finland, Denmark) report increased incidence of brain cancer, US and Swedish ones do not. This inconsistence may be accounted by deficit in reporting of tumors to the Swedish Cancer Registry (Hardell and Carlberg 2009).

Importantly, because the signals are completely replaced by other signals faster then once per 10 years, duration comparable with latent period, epidemiologic studies can not provide basement for assessment of upcoming new signals.

As far as different types of MW signals (carrier frequency, modulation, polarization, far and near field, intermittence, coherence, *etc.*) may produce different effects, cancer risks should ideally be estimated for each MW signal separately. In other words, one type of MW signal would correspond to one chemical compound. That means, for example, that each from 124 signals involved in GSM uplink mobile communication should be separately evaluated to fit situation accepted for estimation of cancer risks from chemical compounds.

It now appears that most, if not all, adult tissues and organs including blood and brain contain stem cells (Metcalfe and Ferguson 2008). Almost all hematopoietic and solid neoplasms arise from cancer stem cells that are dysfunctional versions of a normal stem cells. Current models for radiation carcinogenesis have paid much attention to the stochastic process of energy deposition in cells, but accumulating evidences have shown that the nature of the target cells, i.e. tissue stem cells and progenitor cells, needs to be taken into consideration (Niwa 2010; Richardson 2011). Stem cell self-renewal and progenitor differentiation is regulated by the specialized microenvironment—or "niche"—in which these cells reside (Alvarez-Buylla and Lim 2004) and which regulate stem cells (Morrison and Spradling 2008; Johansson, Cappello et al. 2010; Kim and Shivdasani 2012; Sugiyama and Nagasawa 2012)..Importance of stem cells for carcinogenesis, challenges the definition of volume for SAR determination in safety standards. Instead of random distribution of targets for carcinogenesis, localized distribution of SAR in stem cells and niches is needed. Because very small size of the niches in different tissues including the brain (Kazanis 2012), the SAR averaging should be performed at volumes much less then currently accepted 10 g. Decreasing the sensitive volume to the stem cell niches with sizes down to 10 μm (Richardson 2011) may likely

put almost all mobile phones out of the current safety standards, even given that they are only based on thermal effects and do not consider any other parameters except for SAR. From point view of stem cell organization, the volume of SAR determination may be especially important for setting the safety standards for children. During brain development, most stem cells and their niches are spatially ephemeral and temporally transient as the cellular and molecular "puzzle" behind neurogenesis and morphogenesis is "assembled" and "disassembled" at a dazzling pace. In contrast, in the adult, neural stem cells and their niches are retained in restricted regions with their local developmental processes occurring for the life (Alvarez-Buylla and Lim 2004).

It should be anticipated that some part of the human population, such as children, pregnant women and groups of hypersensitive persons could be especially sensitive to the NT MW exposures.

XXII. CONCLUSIONS

Non-thermal effects of microwaves depend on variety of biological and physical parameters that should be taken into account in setting the safety standards. These exposures can cause health risk. The current safety standards are insufficient to protect from non-thermal microwave effects. Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, is not useful alone for the evaluation of health risks from NT MW of mobile communication. Other parameters of exposure, such as frequency, modulation, duration, dose should be taken into account. New standards should be developed based on knowledge of mechanisms of non-thermal effects. Importantly, because the signals of mobile communication are completely replaced by other signals faster then once per 10 years, duration comparable with latent period, epidemiologic studies cannot provide basement for cancer risk assessment from upcoming new signals. Precautionary Principle should be implemented while new standards are in progress. In many cases, because of ELF modulation and additional ELF fields created by the MW sources, for example by mobile phones, it is difficult to distinguish the effects of exposures to ELF and MW. Therefore, these combined exposures and their possible cancer risks should be considered in combination. It should be anticipated that some part of the human population, such as children, pregnant women and groups of hypersensitive persons could be especially sensitive to the non-thermal microwave exposures.

REFERENCES

Adang D, Remacle C, Vorst AV. 2009. Results of a long-term low-level microwave exposure of rats. IEEE Transactions on Microwave Theory and Techniques 57(10):2488-2497.

Adey WR. 1981. Tissue interactions with nonionizing electromagnetic fields. Physiological Reviews 61:435-514.

Adey WR. 1999. Cell and molecular biology associated with radiation fields of mobile telephones. Review of Radio Science 1996-1999, W R Stone and S Ueno Oxford, Oxford University Press:845-872.

Adey WR, Bawin SM, Lawrence AF. 1982. Effects of weak amplitude-modulated microwave fields on calcium efflux from awake cat cerebral cortex Bioelectromagnetics 3:295-307.

Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. 2008. Effect of cell phone usage on semen analysis in men attending infertility clinic:An observational study Fertility and Sterility 89:124-128.

Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, et al. 2009. Effects of radiofrequency electromagnetic waves .RF-EMW. from cellular phones on human ejaculated semen:an in vitro pilot study Fertility & Sterility 92:1318-1325.

Akoev IG, Pashovkina MS, Dolgacheva LP, Semenova TP, Kalmykov VL. 2002. [Enzymatic activity of some tissues and blood serum from animals and humans exposed to microwaves and hypothesis on the possible role of free radical processes in the nonlinear effects and modification of emotional behavior of animals] Radiatsionnaia Biologiia Radioecologiia 42:322-330.

Alipov ED, Shcheglov VS, Sarimov RM, Belyaev IY. 2003. Cell-density dependent effects of low-dose ionizing radiation on E coli cells. Radiatsionnaia Biologiia Radioecologiia 43:167-171.

Alipov YD, Belyaev IY, Kravchenko VG, Polunin VA, Shcheglov VS. 1993. Experimental justification for generality of resonant response of prokaryotic and eukaryotic cells to MM waves of super-low intensity. Physics of the Alive 1:72-80.

Allis JW, Sinha-Robinson BL. 1987. Temperature-specific inhibition of human red cell Na+/K+ ATPase by 2,450-MHz microwave radiation Bioelectromagnetics 8:203-212.

Alvarez-Buylla A, Lim DA. 2004. For the long run:maintaining germinal niches in the adult brain. Neuron 41:683-686.

Ayata A, Mollaoglu H, Yilmaz HR, Akturk O, Ozguner F, Altuntas I. 2004. Oxidative stress-mediated skin damage in an experimental mobile phone model can be prevented by melatonin. Journal of Dermatology 31:878-883.

Baan R, Grosse y, Lauby-Secretan b, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. 2011. Carcinogenicity of radiofrequency electromagnetic fields Lancet Oncology 12:624-626.

Balci M, Devrim E, Durak I. 2007. Effects of mobile phones on oxidant/antioxidant balance in cornea and lens of rats. Current Eye Research 32:21-25.

Banik S, Bandyopadhyay s, Ganguly S. 2003. Bioeffects of microwave - a brief review. Bioresource Technology 87:155-159.

Bartsch H, Kupper H, Scheurlen U, Deerberg F, Seebald E, Dietz K, et al. 2010. Effect of chronic exposure to a GSM-like signal .mobile phone. on survival of female Sprague-Dawley rats:modulatory effects by month of birth and possibly stage of the solar cycle Neuro Endocrinology Letters 31:457-473.

Beckman KB, Ames BN. 1998. The free radical theory of aging matur. Physiological Reviews 78:547-581.

Belyaev I. 2010. Dependence of non-thermal biological effects of microwaves on physical and biological variables:implications for reproducibility and safety standards European Journal of Oncology - Library NON-THERMAL EFFECTS AND MECHANISMS OF INTERACTION BETWEEN ELECTROMAGNETIC FIELDS AND LIVING MATTER An ICEMS Monograph L Giuliani and M Soffritti Bologna, Italy, RAMAZZINI INSTITUTE, Vol 5:187-218. Available at:http://wwwicemseu/papershtm?f=/c/a/2009/12/15/MNHJ1B49KHDTL

Belyaev IY .1992. Some biophysical aspects of the genetic effects of low intensity millimeter waves. Bioelectrochemistry Bioenergetics 27:11-18.

Belyaev IY. 1993. Biological effects of low dose ionizing radiation and weak electromagnetic fields 7th Workshop on Microdosimetry S G Andreev Suzdal, MIFI Publisher:128-146.

Belyaev IY, Alipov ED. 2001. Frequency-dependent effects of ELF magnetic field on chromatin conformation in Escherichia coli cells and human lymphocytes. Biochimica et Biophysica Acta 1526:269-276.

Belyaev IY, Alipov ED, Harms-Ringdahl M. 1999. Effects of weak ELF on E coli cells and human lymphocytes:role of genetic, physiological and physical parameters. Electricity and Magnetism in Biology and Medicine F Bersani NY, Kluwer Academic:481-484.

Belyaev IY, Alipov YD, Harms-Ringdahl M. 1997. Effects of zero magnetic field on the conformation of chromatin in human cells. Biochimica et Biophysica Acta 1336:465-473.

Belyaev IY, Alipov YD, Matronchik AY. 1998. Cell density dependent response of E coli cells to weak ELF magnetic fields. Bioelectromagnetics 19:300-309.

Belyaev IY, Alipov YD, Matronchik AY, Radko SP. 1995. Cooperativity in E coli cell response to resonance effect of weak extremely low frequency electromagnetic field. Bioelectrochemistry and Bioenergetics 37:85-90.

Belyaev IY, Alipov YD, Polunin VA, Shcheglov VS. 1993. Evidence for dependence of resonant frequency of millimeter wave interaction with Escherichia coli Kl2 cells on haploid genome length Electro- & Magnetobiology 12:39-49.

Belyaev IY, Alipov YD, Shcheglov VS. 1992. Chromosome DNA as a target of resonant interaction between Escherichia coli cells and low-intensity millimeter waves. Electro- & Magnetobiology 11:97-108.

Belyaev IY, Alipov YD, Shcheglov VS, Lystsov VN. 1992. Resonance effect of microwaves on the genome conformational state of E coli cells. Z Naturforsch [C] 47:621-627.

Belyaev IY, Alipov YD, Shcheglov VS, Polunin VA, Aizenberg OA. 1994. Cooperative response of Escherichia coli cells to the resonance effect of millimeter waves at super low intensity. Electro- & Magnetobiology 13:53-66.

Belyaev IY, Eriksson S, Nygren J, Torudd J, Harms-Ringdahl M. 1999. Effects of ethidium bromide on DNA loop organisation in human lymphocytes measured by anomalous viscosity time dependence and single cell gel electrophoresis. Biochimica et Biophysica Acta .BBA. - General Subjects 1428:348-356.

Belyaev IY, Harms-Ringdahl M. 1996. Effects of gamma rays in the 05-50-cGy range on the conformation of chromatin in mammalian cells0 Radiation Research 145:687-693.

Belyaev IY, Hillert L, Protopopova M, Tamm C, Malmgren LOG, Persson BRR, et al. 2005. 915 MHz microwaves and 50 Hz magnetic field affect chromatin conformation and 53BP1 foci in human lymphocytes from hypersensitive and healthy persons. Bioelectromagnetics 26:173-184.

Belyaev IY, Markova E, Hillert L, Malmgren LOG, Persson BRR. 2009. Microwaves from UMTS/GSM mobile phones induce long-lasting inhibition of 53BP1/g-H2AX DNA repair foci in human lymphocytes. Bioelectromagnetics 30:129-141.

Belyaev IY, Shcheglov VS, Alipov ED, Ushakov VL. 2000. Non-thermal effects of extremely high frequency microwaves on chromatin conformation in cells in vitro:dependence on physical, physiological and genetic factors IEEE Transactions on Microwave Theory and Techniques 48.11.:2172-2179.

Belyaev IY, Shcheglov VS and Alipov YD .1992. Existence of selection rules on helicity during discrete transitions of the genome conformational state of Ecoli cells exposed to low-level millimeter radiation. Bioelectrochemistry and Bioenergetics 27:405-411.

Belyaev IY, Shcheglov VS, Alipov YD. 1992. Selection rules on helicity during discrete transitions of the genome conformational state in intact and X-rayed cells of Ecoli in millimeter range of electromagnetic field. In:Charge and Field Effects in Biosystems M Journal of Allen, S F Cleary, A E Sowers and D D Shillady Basel, Switzerland, Birkhauser 3:115-126.

Belyaev IY, Shcheglov VS, Alipov YD, Polunin VA. 1996. Resonance effect of millimeter waves in the power range from 10.-19. to 3 x 10.-3. W/cm^2 on Escherichia coli cells at different concentrations. Bioelectromagnetics 17:312-321.

Belyaev IY, Shcheglov VS, Alipov YD, Radko SP. 1993. Regularities of separate and combined effects of circularly polarized millimeter waves on E coli cells at different phases of culture growth. Bioelectrochemistry and Bioenergetics 31:49-63.

Belyaev SY, Kravchenko VG. 1994. Resonance effect of low-intensity millimeter waves on the chromatin conformational state of rat thymocytes. Zeitschrift für Naturforschung [C] Journal of biosciences 49:352-358.

Betskii OV, Devyatkov ND, Kislov VV. 2000. Low intensity millimeter waves in medicine and biology. Critical Reviews in Biomedical Engineering 28:247-268.

Binhi VN. 2002. Magnetobiology: Underlying physical problems. San Diego, Academic Press.

Binhi VN, Alipov YD, Belyaev IY. 2001. Effect of static magnetic field on E coli cells and individual rotations of ion-protein complexes. Bioelectromagnetics 22:79-86.

Blackman C. 2009. Cell phone radiation:Evidence from ELF and RF studies supporting more inclusive risk identification and assessment. Pathophysiology 16:205-216.

Blackman CF, Benane SG, Elder JA, House DE, Lampe JA, Faulk JM. 1980. Induction of calcium-ion efflux from brain tissue by radiofrequency radiation:effect of sample number and modulation frequency on the power-density window. Bioelectromagnetics 1:35-43.

Blackman CF, Benane SG, Joines WT, Hollis MA, House DE. 1980. Calcium-ion efflux from brain tissue:power-density versus internal field-intensity dependencies at 50-MHz RF radiation. Bioelectromagnetics 1:277-283.

Blank M, Goodman R. 2009. Electromagnetic fields stress living cells. Pathophysiology 16:71-78.

Bolshakov MA, Alekseev SI. 1992. Bursting responses of Lymnea neurons to microwave radiation. Bioelectromagnetics 13:119-129.

Bozhanova TP, Bryukhova AK, Golant MB. 1987. About possibility to use coherent radiation of extremely high frequency for searching differences in the state of living cells Medical and biological aspects of millimeter wave radiation of low intensity. Devyatkov ND , Fryazino IRE. Academy of Science, USSR 280 p:90-97.

Buchner K, Eger H. 2011. Changes of clinically important neurotransmitters under the influence of modulated RF fields - A long-term study under real-life conditions. Original study in German Umwelt - Medizin - Gesellschaft 24:44-57.

Burch JB, Reif JS, Noonan CW, Ichinose T, Bachand AM, KoleberTL, et al. 2002. Melatonin metabolite excretion among cellular telephone users. International Journal of Radiation Biology 78:1029-1036.

Burch JB, Reif JS, Noonan CW, Yost MG. 2000. Melatonin metabolite levels in workers exposed to 60-hz magnetic fields:Work in substations and with 3-phase conductors. Journal of Occupational and Environmental Medicine 42:136-142.

Byus CV, Kartun K, Pieper S, Adey WR. 1988. Increased ornithine decarboxylase activity in cultured cells exposed to low energy modulated microwave fields and phorbol ester tumor promoters. Cancer Research 48:4222-4226.

Byus CV, Lundak RL, Fletcher RM, Adey WR. 1984. Alterations in protein kinase activity following exposure of cultured human lymphocytes to modulated microwave fields. Bioelectromagnetics 5:341-351.

Cam ST, Seyhan N. 2012. Single-strand DNA breaks in human hair root cells exposed to mobile phone radiation. International Journal of Radiation Biology 88:420-424.

Campisi A, Gulino M, Acquaviva R, Bellia P, Raciti G, Grasso R, et al. 2010. Reactive oxygen species levels and DNA fragmentation on astrocytes in primary culture after acute exposure to low intensity microwave electromagnetic field. Neuroscience Letters 473:52-55.

Capri M, Salvioli S, Altilia S, Sevini F, Remondini D, Mesirca P, et al. 2006. Age-dependent effects of in vitro radiofrequency exposure .mobile phone. on CD95+ T helper human lymphocytes. Annals od the New York Academy of Sciences 1067:493-499.

Capri M, Scarcella E, Fumelli C, Bianchi E, Salvioli S, Mesirca P, et al. 2004. In vitro exposure of human lymphocytes to 900 MHz CW and GSM modulated radiofrequency:studies of proliferation, apoptosis and mitochondrial membrane potential. Radiation Research 16:211-218.

Caraglia M, Marra M, Mancinelli F, D'Ambrosio G, Massa R, Giordano A, et al. 2005. Electromagnetic fields at mobile phone frequency induce apoptosis and inactivation of the multi-chaperone complex in human epidermoid cancer cells. Journal of Cell Physiology 204:539-548.

Cardis E, Armstrong BK, Bowman JD, Giles GG, Hours M, Krewski D, et al. 2011. Risk of brain tumours in relation to estimated RF dose from mobile phones:results from five Interphone countries. Occupational & Environmental Medicine 68:631-640.

Chavdoula ED, Panagopoulos DJ, Margaritis LH. 2010. Comparison of biological effects between continuous and intermittent exposure to GSM-900-MHz mobile phone radiation:Detection of apoptotic cell-death features. Mutation Research 700:51-61.

Chiabrera A, Bianco B, Caufman JJ, Pilla AA. 1991. Quantum dynamics of ions in molecular crevices under electromagnetic exposure. In:Electromagnetics in Medicine and Biology, Brighton ct & Pollack SR. San Francisco, San Francisco Press:21-26.

Chiabrera A, Bianco B, Moggia E, Kaufman JJ. 2000. Zeeman-Stark modeling of the RF EMF interaction with ligand binding. Bioelectromagnetics 21:312-324.

Cifra M, Fields JZ, Farhadi A. 2011. Electromagnetic cellular interactions. Progress in Biophysics and Molecular Biology 105:223-246.

Cook CM, Saucier DM, Thomas AW, Prato FS. 2006. Exposure to ELF magnetic and ELF-modulated radiofrequency fields:the time course of physiological and cognitive effects observed in recent studies. 2001-2005. Bioelectromagnetics 27:613-627.

Croft RJ, Chandler JS, Burgess AP, Barry RJ, Williams JD, Clarke AR. 2002. Acute mobile phone operation affects neural function in humans. Clinical Neurophysiology 113:1623-1632.

Czerska EM, Elson EC, Davis CC, Swicord ML, Czerski P. 1992. Effects of continuous and pulsed 2450-MHz radiation on spontaneous lymphoblastoid transformation of human lymphocytes in vitro. Bioelectromagnetics 13:247-259.

Czyz J, Guan K, Zeng Q, Nikolova T, Meister A, Schönborn F, et al. 2004. High frequency electromagnetic fields .GSM signals. affect gene expression levels in tumor suppressor p53-deficient embryonic stem cells Bioelectromagnetics 25:296-307.

d'Ambrosio G, Massa R, Scarfi MR, Zeni O.Schuderer J, Kuster N, Wobus AM. 2002. Cytogenetic damage in human lymphocytes following GMSK phase modulated microwave exposure. Bioelectromagnetics 23:7-13.

Davanipour Z, Sobel E .2009. Long-term exposure to magnetic fields and the risks of Alzheimer's disease and breast cancer: Further biological research. Pathophysiology 16:149-156.

De Iuliis GN, Newey RJ, King BV, Aitken RJ. 2009. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. PLoS One 4:e6446.

Del Vecchio G, Giuliani A, Fernandez M, Mesirca P, Bersani F, Pinto R, et al. 2009. Effect of radiofrequency electromagnetic field exposure on in vitro models of neurodegenerative disease. Bioelectromagnetics 30:564-572.

Devyatkov N.D. 1973. Influence of electromagnetic radiation of millimeter range on biological objects. In Russian. Usp Fiz Nauk 116:453-454.

Devyatkov ND, Golant MB, Betskij OV.1994. Peculiarities of usage of millimeter waves in biology and medicine. In Russian. Moscow, IRE RAN.

Di Carlo A, White N, Guo F, Garrett P, Litovitz T. 2002. Chronic electromagnetic field exposure decreases HSP70 levels and lowers cytoprotection. Journal of Cell Biochem 84:447-454.

Diem E, Schwarz C, Adlkofer F, Jahn O, Rüdiger H. 2005. Non-thermal DNA breakage by mobile-phone radiation .1800 MHz. in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro. Mutation Research 583:178-183.

Dolgacheva LP, Semenova TP, Abzhalelov BB, Akoev IG. 2000. [The effect of electromagnetic radiation on the monoamine oxidase A activity in the rat brain.] Radiatsionnaia Biologiia, Radioecologiia 40:429-432.

Dragicevic N, Bradshaw PC, Mamcarz M, Lin X, Wang L, Cao C, et al. 2011. Long-term electromagnetic field treatment enhances brain mitochondrial function of both Alzheimer's transgenic mice and normal mice:a mechanism for electromagnetic field-induced cognitive benefit? Neuroscience 185:135-49..

Duan Y, Zhang HZ, Bu RF. 2011. Correlation between cellular phone use and epithelial parotid gland malignancies. International Journal of Oral Maxillofacial Surgery 40:966-972.

Dutta SK, Ghosh B, Blackman CF. 1989. Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture. Bioelectromagnetics 10:197-202.

Dutta SK, Subramoniam A, Ghosh B, Parshad R. 1984. Microwave radiation-induced calcium ion efflux from human neuroblastoma cells in culture. Bioelectromagnetics 5:71-78.

Eberhardt JL, Persson BR, Brun AE, Salford LG, Malmgren LO. 2008. Blood-brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones. Electromagnetic Biology & Medicine 27:215-229.

Elhag MA, Nabil GM, Attia AM. 2007. Effects of electromagnetic field produced by mobile phones on the oxidant and antioxidant status of rats. Pakistan Journal of Biological Sciences 10:4271-4274.

Esmekaya MA, Aytekin E, Ozgur E, Güler G, Ergun MA, Omeroğlu S, et al. 2011. Mutagenic and morphologic impacts of 18GHz radiofrequency radiation on human peripheral blood lymphocytes .hPBLs. and possible protective role of pre-treatment with Ginkgo biloba (EGb 761). Science of the Total Environment 410-411:59-64.

Fisher PD, Poznansky MJ, Voss VA. 1982. Effect of microwave radiation .2450 MHz. on the active and passive components of 24Na+ efflux from human erythrocytes. Radiation Research 92:411-422.

Foster KR, Repacholi MH. 2004. Biological effects of radiofrequency fields:does modulation matter? Radiation Research 162:219-225.

Franzellitti S, Valbonesi P, Ciancaglini N, Biondi C, Contin A, Bersani F, et aL. 2010. Transient DNA damage induced by high-frequency electromagnetic fields .GSM 18 GHz. in the human trophoblast HTR-8/SVneo cell line evaluated with the alkaline comet assay. Mutation Research 683:35-42.

Franzellitti S, Valbonesi P, Biondi C, Contin A, Fabbri E. 2008. HSP70 expression in human trophoblast cells exposed to different 18 Ghz mobile phone signals. Radiation Research 170:488-497.

Frei P, Mohler E, Bürgi A, Fröhlich J, Neubauer G, Braun-Fahrländer C, et al. 2010. Classification of personal exposure to radio frequency electromagnetic fields .RF-EMF. for epidemiological research: Evaluation of different exposure assessment methods. Environment International 36:714-720.

Frei P, Mohler E, Neubauer G, Theis G, Bürgi A, Fröhlich J, et al. 2009. Temporal and spatial variability of personal exposure to radio frequency electromagnetic fields. Environmental Research 109:779-785.

French PW, Donnellan M, McKenzie DR. 1997. Electromagnetic radiation at 835 MHz changes the morphology and inhibits proliferation of a human astrocytoma cell line. Bioelectrochemistry & Bioenergetics 43:13-18.

Frey AH. 1967. Brain stem evoked responses associated with low-intensity pulsed UHF energy. Journal of Applied Physiology 23:984-988.

Frey AH. 1974. Differential biologic effects of pulsed and continuous electromagnetic fields and mechanisms of effect. Annals of the New York Academy of Sciences 238:273-279.

Frey AH. 1993. Electromagnetic field interactions with biological systems. FASEB Journal 7:272-281.

Friedman J, Kraus S, Hauptman Y, Schiff Y, Seger R. 2007. Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. The Biochemical Journal 405:559-568.

Frohlich H. 1968. Long-range coherence and energy storage in biological systems. International Journal of Quantum Chemistry 2:641-652.

Gajski G, Garaj-Vrhovac V. 2009. Radioprotective effects of honeybee venom .Apis mellifera. against 915-MHz microwave radiation-induced DNA damage in Wistar rat lymphocytes: in vitro study. International Journal of Toxicology 28:88-98.

Gapeev AB, IakushinaVS, Chemeris NK, Fesenko EE. 1997. Modulated extremely high frequency electromagnetic radiation of low intensity activates or inhibits respiratory burst in neutrophils depending on modulation frequency. In Russian. Biofizika 425:1125-1134.

Gapeev AB, IakushinaVS, Chemeris NK, Fesenko EE. 1999. Dependence of EHF EMF effects on the value of the static magnetic field. Dokl Akad Nauk 369.404-407.

Gapeev AB, IakushinaVS, Chemeris NK, Fesenko EE. 1996. [Modification of the activity of murine peritoneal neutrophils upon exposure to millimeter waves at close and far distances from the emitter.] Biofizika 41:205-219.

Gapeev AB, Mikhailik EN, Chemeris NK. 2008. Anti-inflammatory effects of low-intensity extremely high-frequency electromagnetic radiation: Frequency and power dependence. Bioelectromagnetics 29:197-206.

Gapeev AB, Mikhailik EN, Chemeris NK. 2009. Features of anti-inflammatory effects of modulated extremely high-frequency electromagnetic radiation. Bioelectromagnetics 30:454-61.

Gapeev AB, SafronovaVG, Chemeris NK, Fesenko EE. 1997. Inhibition of the production of reactive oxygen species in mouse peritoneal neutrophils by millimeter wave radiation in the near and far field zones of the radiator. Bioelectrochemistry & Bioenergetics 43:217-220.

Gapeev AB, Yakushina VS, Chemeris NK, Fesenko EE. 1998. Modification of production of reactive oxygen species in mouse peritoneal neutrophils on exposure to low-intensity modulated millimeter wave radiation. Bioelectrochemistry & Bioenergetics 46:267-272.

Gerner C, Haudek V, Schandl U, Bayer E, Gundacker N, Hutter HP, et al. 2010. Increased protein synthesis by cells exposed to a 1,800-MHz radio-frequency mobile phone electromagnetic field, detected by proteome profiling. International Archives of Occupational and Environmental Health 83:691-702.

Golant MB. 1989. Resonance effect of coherent millimeter-band electromagnetic waves on living organisms. In Russian. Biofizika 34:1004-1014.

Golant MB, Kuznetsov AP, Bozhanova TP. 1994. The mechanism of synchronizing yeast cell cultuResearch with EHF-radiation. In Russian. Biofizika 39:490-495.

Golo VL. 2005. Three-wave interaction between interstrand modes of the DNA. Journal of Experimental and Theoretical Physics 101:372-379.

Gos P, Eicher B. Kohli J, Heyer WD. 1997. Extremely high frequency electromagnetic fields at low power density do not affect the division of exponential phase Saccharomyces cerevisiae cells. Bioelectromagnetics 18:142-155.

Grigoriev Y, Nikitina V, Rubtcova N, Pokhodzey L, Grigoriev O, Belyaev I, et al. 2005. The Russian National Committee on Non-Ionizing Radiation Protection .RNCNIRP. and the radiation guidelines Transparency Forum for Mobile Telephone Systems, Stockholm, Available at:http://memberschellose/igorbelyaev/guidelinespdf

Grigoriev YG. 2004. Bioeffects of modulated electromagnetic fields in the acute experiments .results of Russian researches. Annual of Russian National Committee on Non-Ionisng Radiation Protection Moscow, ALLANA:16-73

Grigoriev YG, StepanovVS, Nikitina VN, Rubtcova NB, Shafirkin AV, Vasin VL. 2003. ISTC Report Biological effects of radiofrequency electromagnetic fields and the radiation guidelines. Results of experiments performed in Russia/Soviet Union Moscow, Institute of Biophysics, Ministry of Health, Russian Federation.

Grundler W. 1992. Intensity- and frequency-dependent effects of microwaves on cell growth rates. Bioelectrochemistry & Bioenergetics 27:361-365.

Grundler W, Jentzsch V, Keilmann F, Putterlik V. 1988. Resonant cellular effects of low intensity microwaves. Biological Coherence and Response to External Stimuli H Frцlich Berlin, Springer-Verlag:65-85.

Guler G, Tomruk A, Ozgur E, Sahin D, Sepici A, Altan N, et al. 2012. The effect of radiofrequency radiation on DNA and lipid damage in female and male infant rabbits. International Journal of Radiation Biology 88:367-373.

Guney M, Ozguner F, Oral B, Karahan N, Mungan T. 2007. 900 MHz radiofrequency-induced histopathologic changes and oxidative stress in rat endometrium:protection by vitamins E and C. Toxicology & Industrial Health 23:411-420.

Hardell L, Carlberg M. 2009. Mobile phones, cordless phones and the risk for brain tumours. International Journal of Oncology 35:5-17.

Hardell L , Carlberg M, Hansson Mild K. 2009. Epidemiological evidence for an association between use of wireless phones and tumor diseases. Pathophysiology 16:113-22.

Hardell L, Eriksson M, Carlberg M, Sundström C, Mild KH. 2005. Use of cellular or cordless telephones and the risk for non-Hodgkin's lymphoma. International Archives of Occupational and Environmental Health DOI 101007/s00420-005-0003-5

Hardell L, Mild KH. 2005. Mobile phone use and acoustic neuromas Epidemiology 16:415; author reply 417-418.

Hardell L, Mild KH, Carlberg M. 2003. Further aspects on cellular and cordless telephones and brain tumours. International Journal of Oncology 22:399-407.

Hardell L, Mild KH, Pahlson A, Hallquist A. 2001. Ionizing radiation, cellular telephones and the risk for brain tumours. European Journal of Cancer Prevention 10:523-529.

Hardell L, Mild KH, Carlberg M, Hallquist A. 2004. Cellular and cordless telephone use and the association with brain tumors in different age groups. Archives of Environmental Health 59:132-137.

Heath B, Jenvey S, Cosic I. 1998. Investigation of analogue and digital mobile phone low frequency radiation spectrum characteristics. Proceedings of the 2nd International Conference on Bioelectromagnetism 83-84.

Hinrikus H, Bachmann M, Lass J, Tomson R, Tuulik V. 2008. Effect of 7, 14 and 21 Hz modulated 450 MHz microwave radiation on human electroencephalographic rhythms. International Journal of Radiation Biology 84:69-79.

Hintzsche H, Jastrow C, Kleine-Ostmann T, Stopper H, Schmid E, Schrader T. 2011. Terahertz radiation induces spindle disturbances in human-hamster hybrid cells. Radiation Research 175:569-574.

Hoyto A, Naarala JJ, 2007. Ornithine decarboxylase activity is affected in primary astrocytes but not in secondary cell lines exposed to 872 MHz RF radiation. International Journal of Radiation Biology 83:367-374.

Höytö A, Luukkonen J, Juutilainen J, Naarala J. 2008. Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants. Radiation Research 170:235-243.

Huber R, Treyer V, Borbély AA, Schuderer J, Gottselig JM, Landolt HP, et al. 2002. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking. EEG Journal of Sleep Research 11:289-295.

Huber, R, Treyer V, Schuderer J, Berthold T, Buck A, Kuster N, et al. 2005. Exposure to pulse-modulated radio frequency electromagnetic fields affects regional cerebral blood flow. European Journal of Neuroscience 21:1000-1006.

Huss A, Egger M, Hug K, Huwiler-Müntener K, Röösli M. 2007. Source of funding and results of studies of health effects of mobile phone use:systematic review of experimental studies. Environmental Health Perspectives 115:1-4.

Huttunen P, Hanninen O , Myllyla R. 2009. FM-radio and TV tower signals can cause spontaneous hand movements near moving RF reflector. Pathophysiology 16:201-204.

Hyland GJ. 2000. Physics and biology of mobile telephony. Lancet 356(9244):1833-1836.

IARC. 2002. Biennial Report 2002-2003. Lyon, France, IARC Press 80:183.

ICNIRP. 1998. ICNIRP Guidelines Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields .up to 300 GHz. Health Physics 74:494-522.

Ilhan A, Gurel A, Armutcu F, Kamisli S, Iraz M, Akyol O, et al. 2004. Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain. Clinical Chim Acta 340:153-162.

Ilvonen S, Sihvonen AP, Karkkainen K, Sarvas K. 2005. Numerical assessment of induced ELF currents in the human head due to the battery current of a digital mobile phone. Bioelectromagnetics 26:648-656.

Imge EB, Kilicoglu B, Devrim E, Cetin R, Durak I. 2010. Effects of mobile phone use on brain tissue from the rat and a possible protective role of vitamin C - a preliminary study. International Journal of Radiation Biology 86:1044-1049.

Iskin VD. 1990. Biological effects of millimeter waves and correlation method of their detection. In Russian. Kharkov, Osnova.

Johansson PA, Cappello S, Gotz M. 2010. Stem cells niches during development--lessons from the cerebral cortex. Current Opinions in Neurobiology 20:400-407.

Joines WT, Blackman CF. 1980. Power density, field intensity, and carrier frequency determinants of RF-energy-induced calcium-ion efflux from brain tissue. Bioelectromagnetics 1:271-275.

Jokela K, Puranen L, Sihvonen AP. 2004. Assessment of the magnetic field exposure due to the battery current of digital mobile phones. Health Physics 86:56-66.

Jorge-Mora T, Misa-Agustiño MJ, Rodríguez-González JA, Jorge-Barreiro FJ, Ares-Pena FJ, López-Martín E. 2011. The effects of single and repeated exposure to 245 GHz radiofrequency fields on c-fos protein expression in the paraventricular nucleus of rat hypothalamus. Neurochemical Research 36:2322-2332.

Joseph W, Frei P, Roösli M, Thuróczy G, Gajsek P, Trcek T, et al. 2010. Comparison of personal radio frequency electromagnetic field exposure in different urban areas across Europe. Environmental Research 110:658-663.

Juutilainen J, Hoyto A, Kumlin T, Naarala J. 2011. Review of possible modulation-dependent biological effects of radiofrequency fields. Bioelectromagnetics 32:511-34.

Kabuto M, Nitta H, Yamamoto S, Yamaguchi N, Akiba S, Honda Y, et al. 2006. Childhood leukemia and magnetic fields in Japan:a case-control study of childhood leukemia and residential power-frequency magnetic fields in Japan. International Journal of Cancer 119:643-650.

Kazanis I. 2012. Can adult neural stem cells create new brains? Plasticity in the adult mammalian neurogenic niches:realities and expectations in the era of regenerative biology. Neuroscientist 18:15-27.

Kim TH, Shivdasani RA. 2012. Stem cell niches: famished paneth cells, gluttonous stem cells. Current Biology 22:R579-580.

Kolbun ND, Lobarev VE. 1988. Problems of bioinformational interaction in millimeter range. In Russian. Kibernet Vychislitelnaya Tekhnika 78:94-99.

Koveshnikova IV, Antipenko EN. 1991. [On the quantitative regularities of the cytogenic effect of microwaves] Radiobiologiia 31:149-151.

Köylü H, Mollaoglu H, Ozguner F, Naziroglu M, Delibas N. 2006. Melatonin modulates 900 Mhz microwave-induced lipid peroxidation changes in rat brain. Journal of Toxicology and Industrial Health 22:211-216.

Kundi M, Mild K, Hardell L, Mattsson MO. 2004. Mobile telephones and cancer - a review of epidemiological evidence. Journal of Toxicology & Environmental Health B. Critical Reviews 7:351-384.

Kwee S, Raskmark P. 1998. Changes in cell proliferation due to environmental non-ionizing radiation 2 Microwave radiation. Bioelectrochemistry & Bioenergetics 44:251-255.

Lagroye I, Anane R, Wettring BA, Moros EG, Straube WL, Laregina M, et al. 2004. Measurement of DNA damage after acute exposure to pulsed-wave 2450 MHz microwaves in rat brain cells by two alkaline comet assay methods. International Journal of Radiation Biology 80:11-20.

Lai H. 2004. Interaction of microwaves and a temporally incoherent magnetic field on spatial learning in the rat. Physiology Behavior 82:785-789.

Lai H. 2005. Biological effects of radiofrequency electromagnetic field. Encyclopedia of Biomaterials and Biomedical Engineering. Wnek GE & Bowlin GI, New York, NY, Marcel Decker:1-8.

Lai H, Singh NP. 1995. Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. Bioelectromagnetics 16:207-210.

Lai H, Singh NP. 1996. Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. International Journal of Radiation Biology 69:513-521.

Lai H, Singh NP. 1997. Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. Bioelectromagnetics 18:446-454.

Lai H, Singh NP. 2005. Interaction of microwaves and a temporally incoherent magnetic field on single and double DNA strand breaks in rat brain cells. Electromagnetic Biology & Medicine 24:23-29.

Liburdy RP, Vanek, PF Jr. 1985. Microwaves and the cell membrane II Temperature, plasma, and oxygen mediate microwave-induced membrane permeability in the erythrocyte. Radiation Research 102:190-205.

Liburdy RP, Vanek, PF Jr. 1987. Microwaves and the cell membrane III Protein shedding is oxygen and temperature dependent:evidence for cation bridge involvement. Radiation Research 109:382-395.

Lin-Liu S, Adey WR. 1982. Low frequency amplitude modulated microwave fields change calcium efflux rates from synaptosomes. Bioelectromagnetics 3:309-322.

Linde T, Mild KH. 1997. Measurement of low frequency magnetic fields from digital cellular telephones. Bioelectromagnetics 18:184-186.

Litovitz TA, Krause D, Penafiel M, Elson EC, Mullins JM. 1993. The role of coherence time in the effect of microwaves on ornithine decarboxylase activity. Bioelectromagnetics 14:395-403.

Litovitz TA, Penafiel M, Farrel JM, Krause D, Meister R, and Mullins JM. 1997. Bioeffects induced by exposure to microwaves are mitigated by superposition of ELF noise. Bioelectromagnetics 18:422-430.

Lonn S, Ahlbom A, Hall P, Feychting M. 2004. Mobile phone use and the risk of acoustic neuroma. Epidemiology 15:653-659.

López-Martín E, Bregains J, Relova-Quinteiro JL, Cadarso-Suárez C, Jorge-Barreiro FJ, Ares-Pena FJ. 2009. The action of pulse-modulated GSM radiation increases regional changes in brain activity and c-Fos expression in cortical and subcortical areas in a rat model of picrotoxin-induced seizure proneness. Journal of Neuroscience Research 87:1484-1499.

Lu YS, Huang BT, Huang YX. 2012. Reactive oxygen species formation and apoptosis in human peripheral blood mononuclear cell induced by 900 MHz mobile phone radiation. Oxidative Medicine & Cellular Longevity 2012:740280.

Lukashevsky KV, Belyaev IY. 1990. Switching of prophage lambda genes in Escherichia coli by millimeter waves. Medical Science Research I8:955-957.

Malyapa RS, Ahern EW, Bi C, Straube WL, LaRegina M, Pickard WF, et al. 1998. DNA damage in rat brain cells after in vivo exposure to 2450 MHz electromagnetic radiation and various methods of euthanasia. Radiation Research 149:637-645.

Malyapa RS, Ahern EW, Straube WL, Moros EG, Pickard WF, Roti Roti JL. 1997. Measurement of DNA damage after exposure to 2450 MHz electromagnetic radiation. Radiation Research 148:608-617.

Markkanen A, Penttinen P, Naarala J, Pelkonen J, Sihvonen AP, Juutilainen J. 2004. Apoptosis induced by ultraviolet radiation is enhanced by amplitude modulated radiofrequency radiation in mutant yeast cells. Bioelectromagnetics 25:127-133.

Markovà E, Hillert L, Malmgren L, Persson BR, Belyaev IY. 2005. Microwaves from GSM mobile telephones affect 53BP1 and gamma-H2AX foci in human lymphocytes from hypersensitive and healthy persons. Environmental Health Perspectives 113:1172-1177.

Markovà E, Malmgren LOG, Belyaev IY. 2010. Microwaves from mobile phones inhibit 53BP1 focus formation in human stem cells more strongly than in differentiated cells:possible mechanistic link to cancer risk. Environmental Health Perspectives 118:394-399.

Matronchik AI, Alipov ED, Beliaev IY. 1996. A model of phase modulation of high frequency nucleoid oscillations in reactions of E coli cells to weak static and low-frequency magnetic fields. In Russian. Biofizika 41:642-649.

Matronchik AI, Beliaev IY. 2005. Model of slow nonuniform rotation of the charged DNA domain for effects of microwaves, static and alternating magnetic fields on conformation of nucleoid in living cells. Fröhlich Centenary International Symposium Coherence and Electromagnetic Fields in Biological Systems .CEFBIOS-2005. Journal of Pokorny Prague, Czech Republic, Institute of Radio Engineering and Electronics, Academy of Sciences of the Czech Republic:63-64.

Matronchik AI, Beliaev IY. 2008. Mechanism for combined action of microwaves and static magnetic field: slow non uniform rotation of charged nucleoid. Electromagnetic Biology & Medicine 27:340-354.

Metcalfe AD, Ferguson MW. 2008. Skin stem and progenitor cells:using regeneration as a tissue-engineering strategy. Cellular & Molecular Life Sciences 65:24-32.

Morrison SJ, Spradling AC. 2008. Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. Cell 132:598-611.

Nam KC, Kim SW, Kim SC, Kim DW. 2006. Effects of RF exposure of teenagers and adults by CDMA cellular phones. Bioelectromagnetics 27:509-514.

Nazıroğlu M, Ciğ B, Doğan S, Uğuz AC, Dilek S, Faouzi D. 2012. 245-Gz wireless devices induce oxidative stress and proliferation through cytosolic Ca^{2+} influx in human leukemia cancer cells. International Journal of Radiation Biology 88:449-456.

Nikolova T, Czyz J, Rolletschek A, Blyszczuk P, Fuchs J, Jovtchev G, et al. 2005. Electromagnetic fields affect transcript levels of apoptosis-related genes in embryonic stem cell-derived neural progenitor cells. FASEB Journal 19:1686-1688.

Niwa O. 2010. Roles of stem cells in tissue turnover and radiation carcinogenesis. Radiation Research 174:833-839.

Nylund R, Leszczynski D. 2006. Mobile phone radiation causes changes in gene and protein expression in human endothelial cell lines and the response seems to be genome- and proteome-dependent. Proteomics 6:4769-4780.

Oktem F, Ozguner F, Mollaoglu H, Koyu A, Uz E. 2005. Oxidative damage in the kidney induced by 900-MHz-emitted mobile phone:protection by melatonin. Archives of Medical Research 36:350-355.

Olcerst RB, Belman S, Eisenbud M, Mumford WW, Rabinowitz JR. 1980. The increased passive efflux of sodium and rubidium from rabbit erythrocytes by microwave radiation. Radiation Research 82:244-256.

Oscar KJ, Hawkins TD. 1977. Microwave alteration of the blood-brain barrier system of rats. Brain Research 126:281-293.

Ozguner F, Altinbas A, Ozaydin M, Dogan A, Vural H, Kisioglu AN, et al. 2005. Mobile phone-induced myocardial oxidative stress:protection by a novel antioxidant agent caffeic acid phenethyl ester. Toxicology & Industrial Health 21:223-230.

Ozguner F, Aydin G, Mollaoglu H, Gökalp O, Koyu A, Cesur G. 2004. Prevention of mobile phone induced skin tissue changes by melatonin in rat: an experimental study. Toxicology & Industrial Health 20:133-139.

Ozguner F, Bardak Y, Comlekci C. 2006. Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: a comparative study. Molecular & Cellular Biochemistry 282:83-88.

Ozguner F, Oktem F, Armagan A, Yilmaz R, Koyu A, Demirel R, et al. 2005. Comparative analysis of the protective effects of melatonin and caffeic acid phenethyl ester .CAPE. on mobile phone-induced renal impairment in rat. Molecular & Cellular Biochemistry 276:31-37.

Ozguner F, Oktem F, Ayata A, Koyu A, Yilmaz HR. 2005. A novel antioxidant agent caffeic acid phenethyl ester prevents long-term mobile phone exposure-induced renal impairment in rat. Prognostic value of malondialdehyde, N-acetyl-beta-D-glucosaminidase and nitric oxide determination. Molecular & Cellular Biochemistry 277:73-80.

Ozgur E, Gler G, Seyhan N. 2010. Mobile phone radiation-induced free radical damage in the liver is inhibited by the antioxidants n-acetyl cysteine and epigallocatechin-gallate. International Journal of Radiation Biology 86:935-945.

Pakhomov AG, Akyel Y, Pakhomova ON, Stuck BE, Murphy MR. 1998. Current state and implications of research on biological effects of millimeter waves: a review of the literature. Bioelectromagnetics 19:393-413.

Pakhomov AG, and Murphy MR. 2000. Comprehensive review of the research on biological effects of pulsed radiofrequency radiation in Russia and the former Soviet Union. Advances in Electromagnetic Fields in Living System JC Lin New York, Kluwer Academic/Plenum Publishers 3:265-290.

Pakhomov AG, Murthy PR. 2000. Low-intensity millimeter waves as a novel therapeutic modality. IEEE Transactions on Plasma Science 28:34-40.

Panagopoulos DJ, Karabarbounis A, Margaritis LH. 2002. Mechanism for action of electromagnetic fields on cells. Biochemical & Biophysical Research Communications 298:95-102.

Panagopoulos DJ, Margaritis LH. 2010. The effect of exposure duration on the biological activity of mobile telephony radiation. Mutation Research 699:17-22.

Papageorgiou CC, Nanou ED, Tsiafakis VG, Capsalis CN, Rabavilas AD. 2004. Gender related differences on the EEG during a simulated mobile phone signal. Neuroreport 15:2557-2560.

Pashovkina MS, Akoev IG. 2000a. [Changes in serum alkaline phosphatase activity during in vitro exposure to amplitude-modulated electromagnetic field of ultrahigh frequency .2375 MHz. in guinea pigs] Biofizika 45:130-136.

Pashovkina MS, Akoev IG. 2001b. [Effect of low-intensity pulse-modulated microwave on human blood aspartate aminotransferase activity] Radiatsionnaia biologiia, radioecologiia 41:59-61.

Pashovkina MS, Akoev IG. 2001c. [Effect of low intensity pulse-modulated electromagnetic radiation on activity of alkaline phosphatase in blood serum] Radiatsionnaia Biologiia, Radioecologiia 41:62-66.

Peinnequin A, Piriou A, Mathieu J, Dabouis V, Sebbah C, Malabiau R, et al. 2000. Non-thermal effects of continuous 245 GHz microwaves on Fas-induced apoptosis in human Jurkat T-cell line. Bioelectrochemistry 51:157-161.

Penafiel LM, Litovitz T, Krause D, Desta A, Mullins JM. 1997. Role of modulation on the effect of microwaves on ornithine decarboxylase activity in L929 cells. Bioelectromagnetics 182:132-141.

Perentos N, Iskra S, McKenzie RJ, Cosi I. 2007. Characterization of pulsed ELF magnetic fields generated by GSM mobile phone handsets. World Congress on Medical Physics and Biomedical Engineering 2006, Vol 14, Pts 1-6 14:2706-2709.

Perentos N, Iskra S, McKenzie RJ, Cosi I. 2008. Simulation of pulsed ELF magnetic fields generated by GSM mobile phone handsets for human electromagnetic bioeffects research. Australasian Physical & Engineering Sciences in Medicine 31:235-242.

Persson BRR, Salford KG, Brun A. 1997. Blood-Brain Barrier permeability in rats exposed to electromagnetic fields used in wireless communication. Wireless Networks 3:455-461.

Phillips JL, Singh NP, Lai H. 2009. Electromagnetic fields and DNA damage. Pathophysiology 16:79-88.

Pollycove M, Feinendegen LE. 2003. Radiation-induced versus endogenous DNA damage: possible effect of inducible protective responses in mitigating endogenous damage. Human & Experimental Toxicology 22:290-306.

Postow E, Swicord ML. 1986. Modulated fields and window effects. CRC Handbook of Biological Effects of Electromagnetic Fields C Polk and E Postow Boca Raton, FL, CRC Press:425-460.

Presman AS. 1963. [Problems in the Biological Action of Microwaves] Usp Sovrem Biol 56:161-179.

Presman AS, IuI L, Levitina MA. 1961. [Biological effect of microwaves] Usp Sovrem Biol 51:84-103.

Remondini D, Nylund R, Reivinen J, Poulletier de Gannes F, Veyret B, et al. 2006. Gene expression changes in human cells after exposure to mobile phone microwaves. Proteomics 6:4745-4754.

Repacholi MH, Basten A, Gebski V, Noonan D, Finnie J, Harris AW. 1997. Lymphomas in E mu-Pim1 transgenic mice exposed to pulsed 900 MHZ electromagnetic fields. Radiation Research 1475:631-640.

Richardson RB. 2011. Stem cell niches and other factors that influence the sensitivity of bone marrow to radiation-induced bone cancer and leukaemia in children and adults. International Journal of Radiation Biology 87:343-359.

Salford LG, Brun A, Sturesson K, Eberhardt JL, Persson BR. 1994. Permeability of the blood-brain barrier induced by 915 MHz electromagnetic radiation, continuous wave and modulated at 8, 16, 50, and 200 Hz. Microscopy Research & Technique. 27:535-542.

Sannino A, Sarti M, Reddy SB, Prihoda TJ, Vijayalaxmi, Scarfì MR. 2009. Induction of adaptive response in human blood lymphocytes exposed to radiofrequency radiation. Radiation Research 171:735-742.

Santini R, Seigne M, Bonhomme-Faivre L, Bouffet S, Defrasne E, Sage M. 2001. [Symptoms reported by mobile cellular telephone users] Pathologie-biologie. Paris. 49:222-226.

Sarimov R, Alipov ED, Belyaev IY. 2011. Fifty hertz magnetic fields individually affect chromatin conformation in human lymphocytes:dependence on amplitude, temperature, and initial chromatin state. Bioelectromagnetics 32:570-579.

Sarimov R, Malmgren L, Markova E, Persson B, Belyaev IY. 2004. Non-thermal GSM microwaves affect chromatin conformation in human lymphocytes similar to heat shock. IEEE Transactions on Plasma Science 32:1600-1608.

Schrader T, Münter K, Kleine-Ostmann T, Schmid E. 2008. Spindle disturbances in human-hamster hybrid .AL. cells induced by mobile communication frequency range signals. Bioelectromagnetics 29:626-639.

Schwarz C, Kratochvil E, Pilger A, Kuster N, Adlkofer F, Rüdiger HW. 2008. Radiofrequency electromagnetic fields .UMTS, 1,950 MHz. induce genotoxic effects in vitro in human fibroblasts but not in lymphocytes. International Archives of Occupational Environmental Health 81:755-767.

Sevast'yanova, L A .1981. Nonthermal effects of millimeter radiation. In Russian. Devyatkov ND. Moscow, Institute of Radioelctronics of USSR Academy of Science:86-109.

Shcheglov VS, Alipov ED, Belyaev IY. 2002. Cell-to-cell communication in response of E coli cells at different phases of growth to low-intensity microwaves. Biochimica et Biophysica Acta 1572:101-106.

Shcheglov VS, Belyaev IY, Ushakov VL, Alipov YD. 1997. Power-dependent rearrangement in the spectrum of resonance effect of millimeter waves on the genome conformational state of E coli cells. Electro- & Magnetobiology 16:69-82.

Shckorbatov YG, Grigoryeva NN, Shakhbazov VG, Grabina VA, Bogoslavsky AM. 1998. Microwave irradiation influences on the state of human cell nuclei. Bioelectromagnetics 19:414-419.

Shckorbatov YG, Pasiuga VN, Goncharuk EI, Petrenko TP, Grabina VA, Kolchigin NN, et al. 2010. Effects of differently polarized microwave radiation on the microscopic structure of the nuclei in human fibroblasts. Journal of Zhejiang University Science B 11:801-805.

Shckorbatov YG, Pasiuga VN, Kolchigin NN, Grabina VA, Batrakov DO, Kalashnikov VV, et al. 2009. The influence of differently polarised microwave radiation on chromatin in human cells. International Journal of Radiation Biology 85:322-329.

Sit'ko SP, Ed .1989. The 1st All-Union Symposium with International Participation Use of Millimeter Electromagnetic Radiation in Medicine. Kiev, Ukraine, USSR, TRC Otklik.

Smythe JW, Costall B. 2003. Mobile phone use facilitates memory in male, but not female, subjects. Neuroreport 14:243-246.

Sokolovic D, Djindjic B, Nikolic J, Bjelakovic G, Pavlovic D, Kocic G, et al. 2008. Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. Journal of Radiation Research 49:579-586.

Stagg RB, Thomas WJ, Jones RA, Adey WR. 1997. DNA synthesis and cell proliferation in C6 glioma and primary glial cells exposed to a 83655 MHz modulated radiofrequency field. Bioelectromagnetics 18:230-236.

Sugiyama T, Nagasawa T. 2012. Bone marrow niches for hematopoietic stem cells and immune cells. Inflammation & Allergy Drug Targets 11:201-206.

Sun W, Shen X, Lu D, Fu Y, Lu D, Chiang H. 2012. A 18-GHz radiofrequency radiation induces EGF receptor clustering and phosphorylation in cultured human amniotic (FL) cells. International Journal of Radiation Biology 88:239-244.

Tkalec M, Malarić K, Pavlica M, Pevalek-Kozlina B, Vidaković-Cifrek Z. 2009. Effects of radiofrequency electromagnetic fields on seed germination and root meristematic cells of Allium cepa L. Mutation Research - Genetic Toxicology & Environmental Mutagenesis 672:76-81.

Tkalec M, Malarić K, Pevalek-Kozlina B. 2005. Influence of 400, 900, and 1900 MHz electromagnetic fields on Lemna minor growth and peroxidase activity. Bioelectromagnetics 26:185-193.

Tkalec M, Malarić K, Pevalek-Kozlina B. 2007. Exposure to radiofrequency radiation induces oxidative stress in duckweed Lemna minor L. Science of the Total Environment 388:78-89.

Ushakov VL, Alipov ED, Shcheglov VS, Beliaev IY. 2006. Peculiarities of non-thermal effects of microwaves in the frequency range of 51-52 GHz on E coli cells. Radiatsionnaia Biologiia, Radioecologiia 46:719-728.

Ushakov VL, Shcheglov VS, Beliaev IY, Harms-Ringdahl M. 1999. Combined effects of circularly polarized microwaves and ethidium bromide on E coli cells. Electro- & Magnetobiology 18:233-242.

van Rongen E, Croft R, Juutilainen J, Lagroye I, Miyakoshi J, Saunders R, et al. 2009. Effects of radiofrequency electromagnetic fields on the human nervous system. Journal of Toxicology Environmental Health B Crit Rev 12:572-597.

Veyret B, Bouthet C, Deschaux P, de Seze R, Geffard M, Joussot-Dubien J, et al. 1991. Antibody responses of mice exposed to low-power microwaves under combined, pulse-and-amplitude modulation. Bioelectromagnetics 12:47-56.

Vilenskaya RL, Smolyanskaya AZ, Adamenko VG, Buldasheva ZN, Gelvitch EA, Golant MB, et al. 1972. Induction of the lethal colicin synthesis in E coli K12 C600 .E1. by means the millimeter radiation. In Russian. Bull Eksperim Biol Med 4:52-54.

Webb SJ. 1979. Factors affecting the induction of Lambda prophages by millimetre waves. Physics Letters 73A:145-148.

Yang Y, Jin X, Yan C, Tian Y, Tang J, Shen X. 2008. Case-only study of interactions between DNA repair genes .hMLH1, APEX1, MGMT, XRCC1 and XPD. and low-frequency electromagnetic fields in childhood acute leukemia. Leukemia & Lymphoma 49:2344-2350.

Yao K, Wu W, Yu Y, Zeng Q, He J, Lu D, et al. 2008. Effect of superposed electromagnetic noise on DNA damage of lens epithelial cells induced by microwave radiation. Investigative Ophthalmology & Visual Science 49:2009-2015.

Yao K, Wu W, Yu Y, Zeng Q, He J, Lu D, et al. 2009. Retraction. Effect of superposed electromagnetic noise on DNA damage of lens epithelial cells induced by microwave radiation. Investigative Ophthalmology & Visual Science 50:4530.

Zhao TY, Zou SP, Knapp PE. 2007. Exposure to cell phone radiation up-regulates apoptosis genes in primary culturese of neurons and astrocytes. Neuroscience Letters 412:34-38.

Zmyślony M, Politanski P, Rajkowska E, Szymczak W, Jajte J. 2004. Acute exposure to 930 MHz CW electromagnetic radiation in vitro affects reactive oxygen species level in rat lymphocytes treated by iron ions. Bioelectromagnetics 25:324-328.

Zotti-Martelli L, Peccatori M, Maggini V, Ballardin M, Barale R. 2005. Individual responsiveness to induction of micronuclei in human lymphocytes after exposure in vitro to 18

SECTION 16

Plausible Genetic and Metabolic Mechanisms for the Bioeffects of Very Weak ELF Magnetic Fields on Living Tissues

Paul Héroux, PhD, Professor
Department of Epidemiology, Biostatistics and Occupational Health
McGill University Faculty of Medicine, and
Department of Surgery, InVitroPlus Laboratory
McGill University Health Center
Montreal, Quebec, Canada

Ying Li, PhD
Department of Surgery, InVitroPlus Laboratory
McGill University Health Center
Montreal, Quebec, Canada

Prepared for the BioInitiative Working Group

December 2012

I. INTRODUCTION

A. The "kT Problem"

The biological effects of weak extremely-low frequency (ELF) magnetic fields (MFs) have long been a subject of controversy, with many expressing skepticism as to their very existence: ELF-MFs have lacked a credible mechanism of interaction between MFs and living material.

A prominent conceptual objection has been the "kT problem" (Binhi, 2007). This "problem" can be summarized by the very large ratio between the energy available from a quantum of ELF radiation (2.47×10^{-13} eV) and the thresholds for ionization of atoms (4.34 eV for potassium), chemical activation (~ 0.7 eV), or even the 0.156 eV able to transfer protons across gA channels (Chernyshev, 2002).

What these numbers show is that ELF MFs are certainly not able to have effects through these particular mechanisms, but a detailed theoretical analysis (Binhi, 2007) does not preclude that ELF-MF effects could occur in other ways. MFs can alter the shape of the orbitals of particles without substantially altering their energies, possibly leading to very low thresholds for MF biological effects. Rather than a pure energy problem, as stated above, the true "problem" is to determine if biological structures exist that can be disturbed by very low-amplitude ELF MFs.

II. KEY SCIENTIFIC EVIDENCE

B. Magnetic Sensors

Modern electronics provides interesting examples, such as the MOSFET, where tiny signals can control large energies: a voltage applied to a gate with nominally zero current allows control of substantial drain currents. Biological systems have their own sources of energy, and the MF need only contribute a perturbing influence.

In the context of ELF MF effects, it is useful to examine the transducers of MF-measuring instruments. Induction coils have long been the item of choice for many such instruments, but they suffer from a lack of analogy with possible biological equivalents, in that they gather signal from

substantial surfaces (the coil core), and then concentrate the action of the magnetic flux variations gathered over that considerable area at a single point, the contact of the winding.

Hall-effect probes are closer to the mark, in that they detect the potential difference created by a MF on a current flowing in a semi-conductor. Here, the MF acts to deflect a current flow that is powered by an extraneous source. This device dissociates the energy available from the MF itself from the energy it controls.

Another electronic device even closer to the biological transducer we seek is the Spin Tunnel Junction (Micromagnetics, 2012). Such a junction is made of two ferromagnetic metal layers separated by an insulating barrier of a few nanometers (Fig. 6). If a small voltage is applied across the junction, electrons will tunnel through the barrier, according to the ambient MF. The device's MF sensitivity is based on spin-coherent tunneling: the probability of an electron tunneling across the barrier is dependent on its spin, because an electron of a given spin must tunnel to an unfilled state of the same spin. Even the simplest free-electron descriptions of Spin Polarization and Tunneling MagnetoResistance confirm that junction characteristics are determined not only by the ferromagnetic layers, but depend as well on the properties of the barrier (Tsymbal, 2003). Solid-state Spin Tunnel Junctions can detect MFs as low as 0.26 nT at 60-Hz. What these solid-state devices demonstrate is that very small MFs can have effects within the bulk of materials, and that changes in the properties of insulating materials can affect electron tunneling.

C. Magnetic Fields and Incubators

MF experiments with living cells are immediately faced with a practical problem. Cell culture incubators have within them relatively large MFs, due to their relatively weak attenuation of environmental MFs, and to the necessity of implementing controlled heating, humidity and CO_2 concentration conditions. The first control simulates body temperature, the second avoids osmotic imbalance through evaporation, and the third stabilizes pH values within cell culture media. Table 1 was compiled in a survey of 46 incubators used in research (Su, 2012), and showed that average MFs in water-jacketed CO_2 incubators range from 0.9 to 13 μT.

The reaction of many investigators to this situation has been to compensate for the high backgrounds by using even larger MFs in their experiments. According to the conventional dose-responses expected in Toxicology, the effect of an agent can be detected even in the presence of a background exposure, since the biological response is expected to rise smoothly with dose. Many

investigators must also have felt that more robust data would be obtained using larger exposures, and that background MFs in incubators could be tolerated.

Table 1. Summary MF Table of 46 Surveyed Incubators (in μT).

Brand	Model	Type	Mean	Min	Max	Max Background
New Brunswick	G-25	Shaker	**0.39**	0.2	0.81	2.06*
Chicago Surgical Ele.	N.A.	General	**0.61**	0.25	1.21	3.32*
Forma Scientific	3956	General	**0.76**	0.2	2.64	0.22
Fisher Sci.	Isotemp	General	**0.76**	0.05	1.85	0.32
Fisher Sci.	637D	General	**0.84**	0.22	2.49	0.23
Forma Scientific	3157	CO_2 W	**0.91**	0.11	2.66	1.77*
Thermo Electron	N.A.	Shaker	**0.98**	0.57	1.58	5.86*
Nuaire	US auto flow	CO_2 W	**0.99**	0.4	2.28	1.34*
Thermo Forma	3310	CO_2 W	**1.04**	0.32	3.75	0.68*
Innova New Brunswick	4200	Shaker	**1.17**	0.31	2.97	0.4
Fisher Isotemp	281	General	**1.86**	1.2	2.22	0.47
Baxter	WJ501	CO_2 W	**1.87**	0.77	5.27	1.6*
Sanyo	N.A.	CO_2	**2.77**	0.85	6.72	0.3
New Brunswick	G-25	Shaker	**2.79**	0.42	16.13	0.31
Sanyo O_2/ CO_2	MCO-18M	CO_2	**2.8**	1.48	4.14	0.81*
Sanyo	MCO_19AIC	CO_2	**2.94**	1.63	5.17	3.31*
Sanyo	MCO-20AIC	CO_2	**3.12**	1.22	6.64	6.68*
Hera Cell	240	CO_2	**3.28**	2.36	4.62	1.48*
Baxter	Tempcon	General	**3.36**	0.61	7.43	1*
Innova New Brunswick	4000	Shaker	**3.47**	1.27	9.53	0.36
Hera Cell	N.A.	CO_2	**3.65**	2.68	4.49	0.26*
Thermo Scientific	370	CO_2	**3.84**	1.9	7.01	0.64*
New Brunswick	C25	Shaker	**3.88**	0.33	17.74	0.96*
Thermo Electron	3110	CO_2 W	**3.91**	1.19	8.56	0.92*
Nuaire	Nu4750	CO_2 W	**3.95**	0.77	10.38	0.64*
Thermo Scientific	370	CO_2	**3.99**	2.03	6.25	0.96*
Forma Scientific	3130	CO_2 W	**4.67**	1.53	11.14	1.37*
Forma Scientific	3110	CO_2 W	**5.44**	1.77	12.59	2.42*
Fisher Sci.	546	CO_2 W	**6.58**	2.36	16.88	0.38
Forma Scientific	N.A.(Old)	CO_2	**6.71**	2.32	16.83	1.36*
Thermo Electron	3130	CO_2 W	**6.79**	1.73	16.97	18.9***
Thermo Electron	3110	CO_2	**7.55**	1.83	18.28	3.92*
Revco	N.A.(Old)	CO_2	**7.67**	3.57	17.76	1.27*
Napco	3550	CO_2	**7.8**	3.52	13.42	2.84*
Thermo Electron	Napco 3550	CO2	**7.83**	3.81	12.13	1.63*
Fisher Sci.	Isotemp 546	CO_2 W	**9.61**	2.34	37.58	0.76*
Thermo Forma	3110	CO_2 W	**9.73**	2.73	24.14	0.47*
N.A.	N.A.	General	**10.46**	3.57	19.51	0.2

Thermo Forma	3110	CO_2 W	**11.89**	3.3	30.41	0.49*
Gallenkamp	N.A.	General	**11.96**	3.06	37.17	2.3*
Fisher Sci.	610	CO_2	**12.3**	5.15	35.52	1.59*
Forma Scientific	3158	CO_2 W	**13.08**	2.62	50.64	1.61*
Labline	3527	Shaker	**14.04**	3.62	42.74	11.87**
WWR international	2005	General	**15.48**	4.92	47.37	1.28
Forma Scientific	546	CO_2	**16.5**	2.61	74.47	3.45*
Sanyo	MIR152	CO_2	**26.98**	5.67	120	0.34*

Type "CO_2 W" means CO_2 incubator with water jacket. "Max Background" refers to measurements outside the incubators. * measured at 50 cm or halfway between the incubator and other electric equipment. ** 5 cm to another incubator. *** 10 cm to a power outlet panel. For more details, refer to Dong and Héroux, 2012.

D. Magnetic Shielding

If it is desired to eliminate the background MFs of incubators to low levels, shielding must be implemented within the incubators. We achieved this in our own experiments using structural steel cylinders 6.3 mm in thickness. As shown in Fig. 1, culture vessels are centered in concentric rectangular structural steel pipes 5.1 x 7.6 x 20 cm, 7.6 x 10.2 x 20 cm and 15.2 x 24.5 x 36 cm. This configuration reduces 60-Hz MFs by a factor of 144, providing "unexposed" cells with a MF environment of 3 nT, slightly below the measurement floor (5 nT at 60-Hz) of our Narda EFA-300 MF instrument (Li, 2012a). The shielding weighs about 20 kg, and is subject to corrosion, if used in the incubator for long periods of time. Fig. 2 shows the change along the axis of the shielding in the triaxially integrated MF. Static MFs within the shields are slightly lower than 50 µT, as structural steel is de-magnetized during production, but of random direction.

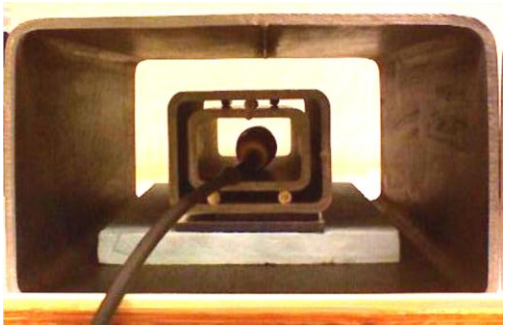

Fig. 1. The three layers of magnetic shielding. The Narda EFA-300's MF probe is in place of the culture vessel. MF coils for exposure are below, but not in contact with the two smaller shields, insulated from the outer shield by a layer of rigid foam.

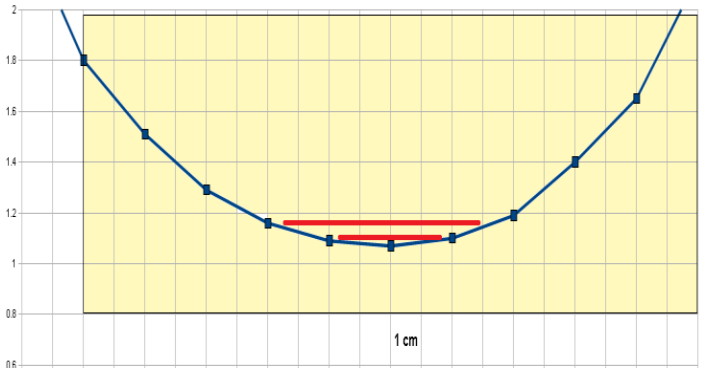

Fig. 2. MF density (μT) generated by an exposure coil vs longitudinal distance inside a magnetic shield pair. The two red lines show the extent of T-25 and T-12 culture vessels, and the yellow rectangle is the smaller shield outline.

E. Experiments on Cells

We conducted experiments on 5 cancer cell lines, with the objective of bringing high precision to our *in vitro* determinations. This objective was reached using automated data acquisition and real-time computer vision, which allowed automated recognition of cells, apobodies and decay particles in cell cultures (Héroux, 2004). In order to reduce deviations related to changing cell culture media, our work used a single synthetic medium (rather than Fetal Bovine Serum) for all 5 cancer models investigated (Li, 2012b).

We first focused our work on changes in the behavior of our cell models under various levels of oxygen. Somewhat surprisingly, all 5 models survived even under anoxic (0 % oxygen) conditions, confirming the exceptional flexibility of cancers cells, able to thrive under anoxia, presumably by finding glycolysis-based sources of cellular energy even in the absence of oxygen.
Low oxygen conditions are actually quite representative of the normal environment of many cells in the body, and are certainly a better *in vitro* representation of the environment of tumor cells, which grow in oxygen and nutrient-restricted environments.

Withdrawal of oxygen suppresses metabolism, as a major combustible of mitochondrial ATP synthesis, oxygen, is eliminated. Metabolism can also be suppressed by a number of chemicals such as oligomycin, imatinib and melatonin-vitamin C, which we collectively designated as “metabolic restrictors”.

F. Karyotype Contraction

When grown under *anoxia* (as opposed to *atmoxia* which is 21 % oxygen, and the commonly used cell culture condition) our 5 cancer cell models lost 6 to 8 chromosomes from their normal

number (Table 3). Further, in the presence of strong doses of antioxidant metabolic restrictors, the cell lines quickly reverted to almost normal chromosome numbers (47 – 49). The anoxic cells showed increases in proliferation rate, and the acquisition of a stable, stem phenotype.

Using our 5 hyperploid (54 – 69 chromosomes) cancer cell models, we found that our cells adjusted their chromosome numbers up or down, to match their micro-environment, through rapid mechanisms of endo-reduplication (unscheduled, extra-mitotic chromosome duplication) or chromosome loss. We called this reversible loss of chromosomes under suppressed metabolism "Karyotype Contraction" (KC).

Anoxic K562 displays a very stable karyotype, with 75 % of the cells having either 61 or 62 chromosomes. With the knowledge that metabolic changes would change these chromosome counts, we then set out to investigate the effects of ELF MFs on this model, while we carefully controlled MFs using the shielding techniques described above. We were then using KC as a metabolic scale.

Starting from cell cultures maintained in a pre-industrial environment (less than 4 nT 60-Hz MF), our 5 cancer cell lines were exposed to constant ELF-MFs within the range of 0.025 to 5 μT, and the cells were examined for karyotype changes after 6 days.

As shown in Table 2, all cancer cells lines lost chromosomes from MF exposures, with a mostly flat dose-response. It seemed that the number of chromosomes lost was more specifically connected to the particular cell type than to the MF level, although the two erythro-leukemia cell types both showed a dose-response between 25 and 400 nT.

Surprisingly, constant MF exposures for three weeks allowed a rising return to the baseline, unperturbed karyotypes. From this point, small MF increases or decreases (10 %) were then again capable of inducing karyotype contractions (Li, 2012a).

Table 2. Karyotype Contraction (mean number of chromosomes lost over 6 days)

Magnetic Field (nT)	Anoxic K562 Erythroleukemia	Atmoxic HEL Erythroleukemia	Atmoxic NCI-H460 Lung cancer	Anoxic MCF-7 Breast cancer	Atmoxic COLO-320DM Colon cancer
25	2.21				
50	4.92	10.22	7.52	11	5.36
100	8.18	11.55			
200	11.04				

400	10.4	12.79	7.55	10.64	5.85
700	9.52				
1000	7.69			10.68	
1500	9.94				
5000	12.1	13.03	7.46	10.95	5.78

Table 3. Karyotype Contraction (mean number of chromosomes lost over 6 days)

Cell	Atmoxic Modal Chromosome Number	Anoxic KC	Anoxic to MF Saturation KC	Atmoxic to MF Saturation KC	Atmoxic to Anti-Oxidant Suppression KC*
K-562 Erythroleukemia	69	7	10.12		21.34
HEL Erythroleukemia	66	7		12.91	18
MCF-7 Breast cancer	82	8	10.82		18
NCI-H460 Lung cancer	57	6		7.51	10
COLO-320DM Colon cancer	54	6		5.66	7.7
Average	*65.6*	*6.8*	*10.47*	*8.69*	*15.01*
Condition	+ O_2	- O_2	- O_2 + MFs	O_2 + MFs	O_2 + Oxidative Inhibition

The conclusion from these observations was that MFs act as a metabolic inhibitor, even at very low levels commonly encountered in the normal environment.

G. ATP Synthase

Supplementary tests carried out by comparing MF-exposed cell cultures to cultures exposed to various metabolic suppressors showed that the MF-exposed cultures were remarkably similar to those exposed to oligomycin A, a specific inhibitor of the Fo segment of the enzyme ATP Synthase (ATPS).

But how could MFs as low as 25 nT alter the activity of ATPS? ATPS has the structure of a motor-generator than normally produces ATP using the energy of a flow of protons through a turbine-like structure, Fo. MFs apparently impaired the flow of protons through ATPS Fo.

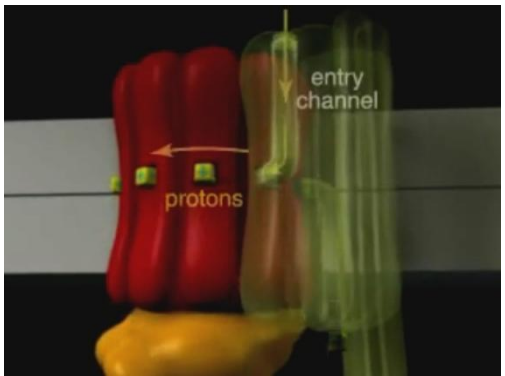

Fig. 3. The structure of ATPS Fo: entry and exit channels for the movement of protons (Yoshida, Tokyo Institute of Technology).

Russian physicists (Semikhina 1981; Semikhina 1988) have reported that very low levels of ELF MFs (25 nT) can alter the structure of water, and that the effects of the altered water structure would be particularly important under high concentrations of protons and water molecules. An interesting aspect of these changes in water structure is that the transition between states takes several hours.

As it turns out, the entry and exit channels of ATPS Fo (Fig. 3) are hydrophilic channels, which means that they are expected to be filled with water molecules, and the intermembrane potential of mitochondria maintains a large electric field (180 kV/cm) which concentrates protons within them. These locations seem ideal to embody the low level effects documented by Semikhina and Kiselev.

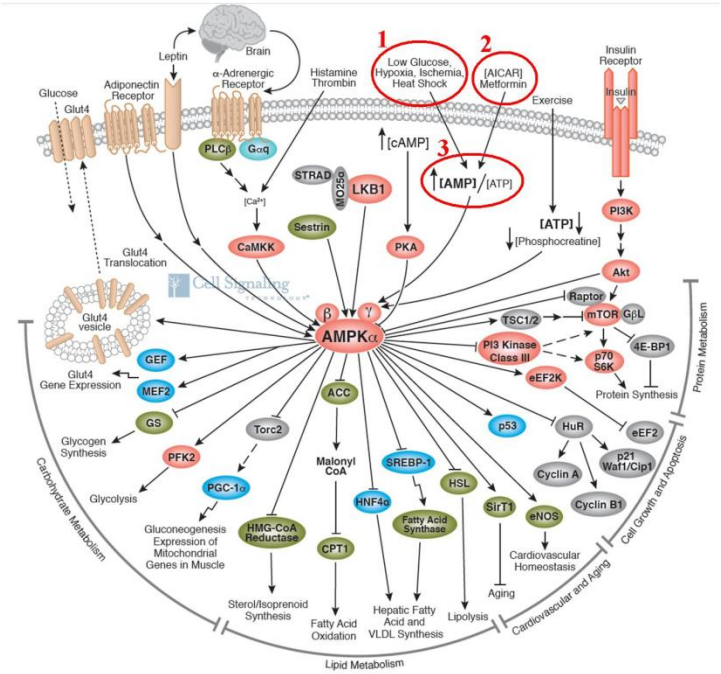

Fig. 4. The many regulatory pathways of AMPK, with the hypoxic (1), metformin (2) and ATPS suppression sites (3) labeled (http://www.cellsignal.com/).

H. AMPK

If the mechanism was indeed as we thought, then MFs would alter the production of ATP in cells. If this happened, another important intracellular enzyme, AMP-activated protein kinase (AMPK), would

immediately be activated, as AMPK is extremely sensitive to changes in the level of ATP. We tested this hypothesis by two supplementary assays involving metformin and resistin. As expected, MF effects were amplified by metformin, an AMPK stimulator, and attenuated by resistin, an AMPK inhibitor (Li, 2012a).

Our data therefore suggests that the karyotype contractions caused by MFs stem from interference with mitochondria's ATP synthase (ATPS), compensated by the action of AMPK. The involvement of AMPK also conveniently explains the slow restoration of karyotypes to their original level after 3 weeks, as AMPK is not only fast-acting to restore ATP levels, but slow-acting through its numerous metabolic and genetic regulation pathways (Fig. 4). It may also explain the unusual observation where increases or decreases in MF exposures can both produce KCs (Li, 2012a).

I. In the Channels

Some enzymes operate faster than predicted by classical thermodynamics, and their increased speed can be explained by tunneling of protons or electrons through activation barriers (Garcia-Viloca, 2004; Olsson, 2004). Quantum tunneling for protons over 6 nm through bridging by water molecules has been observed in tryptamine oxidation by aromatic amine dehydrogenase, for example, and tunneling in enzymatic reactions is now widely accepted in biological models (Masgrau, 2006).

It is of interest to examine how protons may flow through ATPS Fo channels. The protons trickle through a thin pipe of water molecules, propelled by an electric field of about 180 kV/cm. Adiabatic tunneling should be more efficient than non-adiabatic coupling, implying that disturbances along the channel could result in loss of channel transparency. Proton-coupled electron transfer underpins many biological reactions, and may occur as unidirectional or bidirectional, and synchronous or asynchronous, transfer of protons and electrons (Reece, 2009).

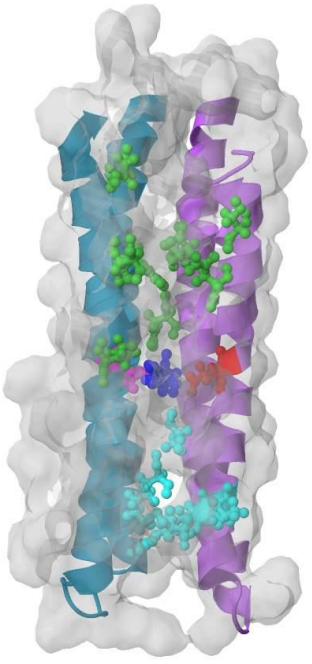

Fig. 5. The ATPS Fo proton hydrophilic channel. Hydrophilic side chains and residues are in green and blue. (from Sasada R, Marcey D. ATP Synthase, 2010. http://www.callutheran.edu/BioDev/omm/jmolxx/atp_synthase/atp_synthase.html#fig1).

It is probable that both electrons and protons tunnel through the channel, making theoretical analysis more complex, especially as electrons meet with different protons along a chain. Since protons are much heavier than electrons (x1836), their wavelength is 43 times shorter (inverse square root), and electrons may transfer over longer distances (Moser, 1992; Gray, 1996). Thus, electron transfer can span fractions of nano-meters, while proton transfer occurs mostly within a hydrogen bond (less than 0.197 nm). The hydrogen bond strength (23.3 kJ/mol) is just 5 times the average thermal fluctuation energy. Quantum chemical calculations show that this strength can vary as much as 90 %, depending on the level of cooperativity or anti-cooperativity within water molecule chains, which corresponds to a bond length change of 9 %, or 0.018 nm (Hus, 2012).

This limited reach of proton tunneling and its delicate dependence on water cluster structure may be major factors underlying the sensitivity of ATPS performance to MF-exposed water.

J. Water 'Remanence'

From our observations, particularly the fact that exposed cell culture medium can retain memory of past MF exposures (Li, 2012a), it does not appear that biological effects of MFs, as we detected them, are based on a direct interaction with electrons or protons, but rather, as suggested by Semikhina and Kiselev, on an interaction between MF and the structure of water, which in turn influences electron and proton tunneling. The exact structure of the water molecule arrays responsible is not known, but may be connected with long-lived hydrogen bond structures which confer particular proton transparency to ATPS Fo water channels. This structure seems vulnerable to interference by MFs over a wide range of intensities and possibly frequencies (Kiselev, 1988). Perturbations to the structure of O-H bond vibrations has even been spectroscopically detected as slow (hours) transitions in water exposed to sunlight radiation (Yokono, 2009).

This would not be the first instance of subtle changes in hydrogen bonds resulting in large influences in biology. A contemporary example relates to the selective uptake of phosphorus rather than arsenic by bacteria. The discrimination by a factor of 4,500 in phosphorus vs arsenic is based on a 4 %

distortion in a unique low-barrier hydrogen bond (Elias, 2012).

III. DISCUSSION

There are similarities as well as differences between semi-conductor tunneling and ATPS tunneling. Both involve oxygen; tunneling distances, as well as the voltages applied (Fig. 6) are similar. But in semiconductor tunneling, only electrons are mobile, while protons move within ATPS. In the semiconductor, magnetic sensing is mainly through shifts in the populations of electrons with a given spin, determined by the electrodes. In ATPS, the transparency of the water channel seems determined by long-term MF exposures.

Perhaps least understood is how cells can metabolically compensate for various MF exposures over time, as shown by the restoration of their chromosome numbers after three week exposures (Li, 2012a). Anoxia leads to permanent KCs, but other KCs from MFs or other anti-oxidants are transient. Most anti-oxidant and MF KCs are larger than the atmoxic to anoxic transition KCs, possibly because some oxygen is still available to cell metabolism, even under anoxic conditions. Anoxia and MFs together are effective metabolic suppressors.

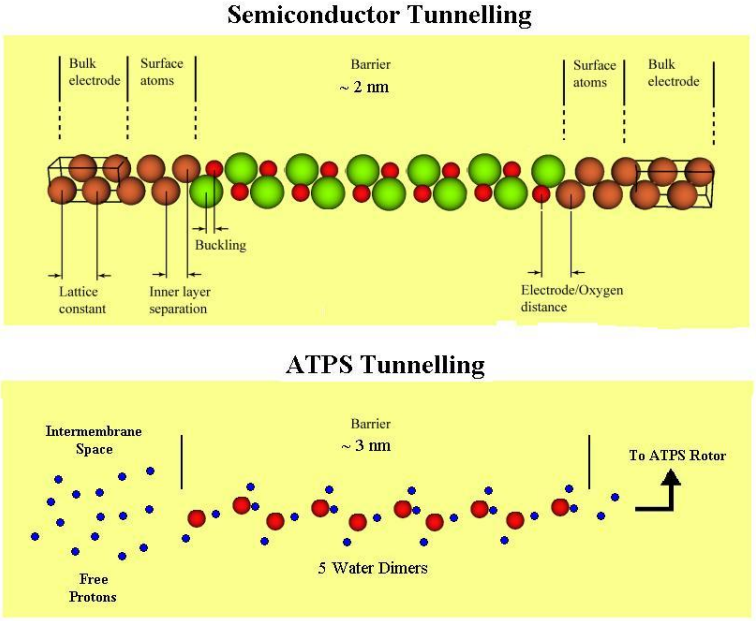

Fig. 6 Tunneling in magnetic sensors and in ATPS water channels.

IV. CONCLUSIONS

The particularities of hydrogen bond structures in water can justify the subtle changes detected in water structure under MF exposures. Under specific circumstances, such water changes may influence the flux of protons in ATPS channels, thus inducing some biological effects of MFs. These interactions seem to involve very small energies, and also seem to require hours to establish themselves, thus bypassing the celebrated "kT problem". These results may be environmentally important, in view of the central roles played in human physiology by ATPS and AMPK, particularly in their links to diabetes, cancer and longevity (Li, 2012a). The wide range of MF amplitudes and frequencies that can potentially disturb ATPS make this effect a global health issue. Although society seems to compile diseases with more enthusiasm that longevity (Li, 2012a), it should be remembered that MF exposures may have both undesirable and desirable effects on health.

V. REFERENCES

Binhi VN, Rubin AB. Magnetobiology: The kT paradox and possible solutions. Electromagnetic Biology and Medicine 2007; 26: 45-62.

Chernyshev A, Cukierman S. Thermodynamic view of activation energies of proton transfer in various gramicidin a channels. Biophysical Journal 2002;82;182-192.

Elias M, Wellner A, Goldin-Azulay K, Chabriere E, Vorholt JA, Erb TJ, http://www.ncbi.nlm.nih.gov/pubmed?term=Tawfik DS%5BAuthor%5D&cauthor=true&cauthor_uid=23034649 et al. The molecular basis of phosphate discrimination in arsenate-rich environments. Nature. 2012;491(7422):134-7.

Garcia-Viloca M, Gao J, Karplus M, Truhlar DG. How enzymes work: analysis by modern rate theory and computer simulations. Science 2004;303 (5655):186-95.

Gray HB, Winkler JR. Electron transfer in proteins. Annu. Rev. Biochem. 1996 65 :537-61.

Héroux P, Kyrychenko I, Bourdages M. Proliferation and apoptosis rate of living erythroleukemia cells, Microscopy and Analysis 2004;18 (3):13-15 (UK).

Huš M, Urbic T. Strength of hydrogen bonds of water depends on local environment, J. Chem. Phys. 2012;136 (2012) 14, 144305-311.

Kiselev VF, Saletskii AM, Semikhina LP. Influence of weak magnetic fields and UHF radiation on certain dielectric and optical properties of water and aqueous solutions. Translated from Teoreticheskaya i Eksperimental'naya Khimiya 1988;24(3):330-334.

Li Y, Héroux P. Extra-low-frequency magnetic fields alter cancer cells through metabolic restriction, 2012a. Available at: http://arXiv.org/abs/1209.5754

Li Y, Héroux P, Kyrychenko I. Metabolic Restriction of cancer cells in vitro causes karyotype contraction - an indicator of cancer promotion? Tumor Biology 2012;33(1):195-205.

Masgrau L, Roujeinikova A, Johannissen LO, Hothi P, Basran J, Ranaghan KE, et al. Atomic description of an enzyme reaction dominated by proton tunneling. Science 2006;312 (5771): 237–41.

Micromagnetics, 2012. Available at: http://micromagnetics.com/docs/SpinTJ_TMR_magnetic_sensors_brochure.pdf)

Moser CC, Keske JK, Warncke K, Farid RS, Dutton PL. Nature of biological electron transfer. Nature. 1992;355(6363):796-802.

Olsson MH, Siegbahn PE, Warshel A. Simulations of the large kinetic isotope effect and the temperature dependence of the hydrogen atom transfer in lipoxygenase. Journal of the American Chemical Society 2004;126 (9): 2820=2828.

Reece SY, Nocera DG. Proton-coupled electron transfer in biology: results from synergistic studies in natural and model systems. Annual Review of Biochemistry 2009;78: 673-699).

Semikhina LP, Kiselev VF. Effect of weak magnetic fields on the properties of water and ice. Russian Physics Journal 1981;31:5351-5354.

Semikhina LP, Kiselev VF, Levshin LV, Saletskii AM. Effect of weak magnetic fields on the luminescence-spectral properties of a dye in an aqueous solution. Journal of Applied Spectroscopy 1988 ;48:556-559.

Su D, Héroux P. Survey of extra-low frequency and very-low frequency magnetic fields in cell culture incubators, 2012. Available at: http://arxiv.org/abs/1211.2458

Tsymbal EY, Mryasov ON, LeClair PR. Spin-dependent tunneling in magnetic tunnel junctions. Evgeny Tsymbal Publications. Paper 19, 2003. Available at: http://digitalcommons.unl.edu/physicstsymbal/19

Yokono T, Shimokawa S, Yokono M, Hattori H. Infra-Red Spectroscopic study of structural change of liquid water induced by sunlight irradiation. 2009;Water 1(29-34).

SECTION 17

Electromagnetic Medicine

Non-Inductive Non-Thermal Modalities

(Supplement 2012)

Abraham R. Liboff, PhD, Professor Emeritus

Department of Physics

Oakland University

Rochester Hills, Michigan USA

Prepared for the BioInitiative Working Group

September 2012

I. INTRODUCTION

The area of electromagnetic medicine (EM) encompasses the applications of electricity and magnetism to medical practice. Although this includes both diagnostic and therapeutic applications, the medical community is far more familiar with the former, notably with techniques such as magnetic resonance imaging (MRI), electromyography (EMG), electroencephalography (EEG), electrocardiography (EKG), and magnetocardiography (MKG). There are historical reasons for the medical unfamiliarity (even antipathy) with electromagnetically-based therapies. One has only to look at the beginnings of modern medicine in the United States, specifically the 1910 Flexner report [1,2] that provided the basis for medical education today. Prior to this report there was widespread use of electromagnetic techniques in medicine, often little more than late 19th century versions of snake-oil cures. In great measure the present aversion to electromagnetic therapies built into modern medicine is a direct result of Victorian age quackery.

Another reason for this antipathy, apart from the constraint on the teaching curriculum, has been the extraordinary success of, first, the germ theories of Pasteur and Koch, and, second, the development of molecular biology following the work of Watson and Crick. These have engendered a sense of completeness, a feeling that there is no place for alternate, radically new approaches to the way that illness is treated. Even when electromagnetically-based therapies have proven beneficial, they have been usually ignored. There is little impetus to replace the existing approach, since it is firmly believed that nothing is more fundamental than the existing paradigm, that questions of wellness and illness are ultimately biochemical in nature.

The divisions in electromagnetic medicine are outlined in Fig. 1. Beyond the separation into diagnostic and therapeutic applications another distinction is made for applications of weak-field ELF magnetic in the treatment of illness. The description ***non-inductive non-thermal*** helps emphasize that the effects obtained by applying low intensity low-frequency electromagnetic fields to biological systems are not the result of either inductive emf generation or the delivery of thermal energies through Joule heating. By contrast, a number of clinical devices that make use of Faraday induction or Joule heating are recognized by the medical community not only because

they are effective, but also because the applied voltages, currents or heat are fully consistent with what is expected biochemically. In sharp contrast, the non-inductive non-thermal category includes clinical applications where this is not true, that is, where the electromagnetic variables that are part of the therapy fall outside those permitted by the current medical paradigm.

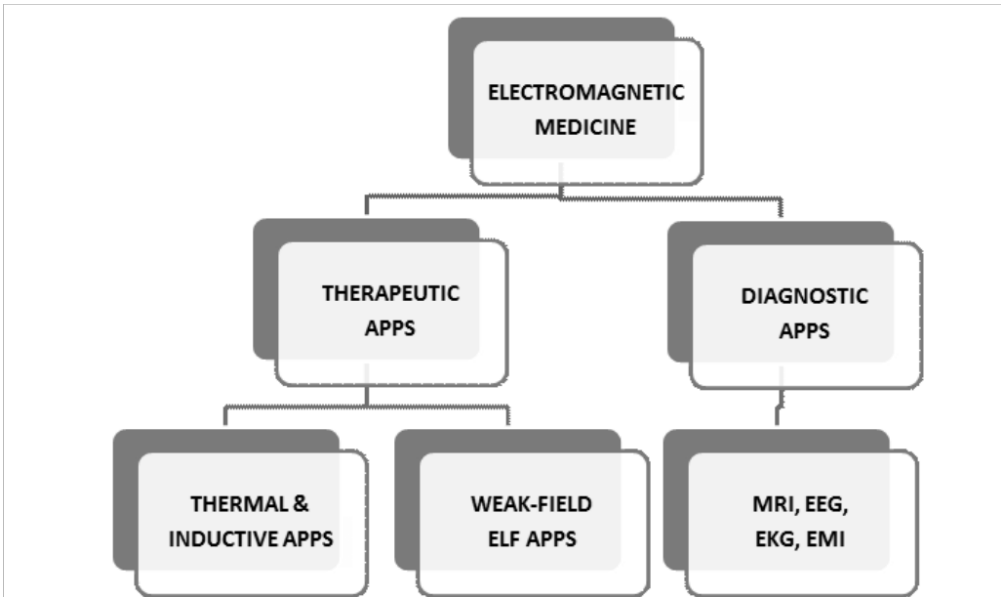

Fig. 1. Divisions comprising Electromagnetic Medicine

II. WEAK-FIELD ELF APPLICATIONS: SCIENTIFIC BASIS

There is a wealth of evidence showing that weakly intense ELF fields affect the metabolic responses in cells. It was found in the 1980s that ELF magnetic fields too weak to be considered as inductive sources of potential differences are nevertheless capable of affecting DNA synthesis in mammalian cell culture[3,4]. Since that time, there have been numerous reports (Table 1) that magnetic fields on the order of several microTesla and in the 3-300 Hz ELF frequency range can affect a wide range of biological systems. A short list of such reports, given in Table 1, emphasizes both the variety of systems in which these effects have been found, and the difficulty in providing an explanation, as evidenced by the fact that these studies have a history extending back more than 25 years. The lack of a reasonable explanation is not a trivial distinction, since there is great reluctance to accept observational evidence, regardless of replications and the number of supportive reports, without a reasonable biomolecular basis

Biological Model	YEAR	Reference
Rat behavior	**1986**	**Thomas et al[5]**
Diatom motility	**1987**	**Smith et al[6]**
Protein synthesis in salivary gland cells	**1988**	**Goodman and Henderson[7]**
Mitogenesis in lymphocytes	**1989**	**Cossarizza et al[8]**
Production of glycosaminoglycans in cartilage	**1991**	**Smith et al[9]**
Neuroblastoma cell metabolism	**1992**	**Smith et al[10]**
Expression of Insulin Growth Factor II	**1995**	**Fitzsimmons et al[11]**
Regeneration of planarians	**1995**	**Jenrow et al[12]**
Analgesia in snails	**1996**	**Prato et al[13]**
Rat EEG	**1998**	**Vorobyov et al[14]**
Growth Rate in plants	**2005**	**Galland and Pazur[15]**
Stem cell differentiation	**2009**	**Gaetini et al[16]**

Table 1. List of reports indicating that non-inductive ELF magnetic fields are biologically interactive. Note that these reports are by no means isolated. A number of these have been independently replicated, for example the studies on rat behavior, lymphocytes, planarians, and plants.

In 1998 a group led by Zhadin[17] discovered that these effects are also found at much lower intensities. AC magnetic fields as low as 40 nT can shift the electrical conductivity of polar amino acids in aqueous solutions. This work, independently replicated[18,19,20], is typified by a sharp change in conductivity at one specific frequency, as shown in Fig. 2. The explanation for this remarkable effect makes use of quantum electrodynamics to provide a means of reducing the viscosity of water sufficiently to allow Lorentz forces to be observed on solvated biological ions, thereby establishing a straightforward reason for the many difficult-to-explain magnetic stimulation reports claiming a connection to ion cyclotron resonance[21].

Ion cyclotron resonance (ICR) as it applies to biological systems was first discovered[22,23] to be a critical underlying factor in connection with previously observed[24] electromagnetically-induced changes in free calcium in brain tissue (Ca-efflux experiments). In the presence of a static magnetic field the most prominent effects are always observed for parallel AC magnetic fields with frequencies very close to the cyclotron frequency of the calcium ion. The majority of subsequent ICR cellular studies have focused on the Ca^{2+} ion. As a second messenger it is involved in regulation at all stages of growth and development, including proliferation, and in the organization of cytoskeletal elements. Indeed some of the results shown in Table 1 are examples of Ca^{2+} ICR stimulation.

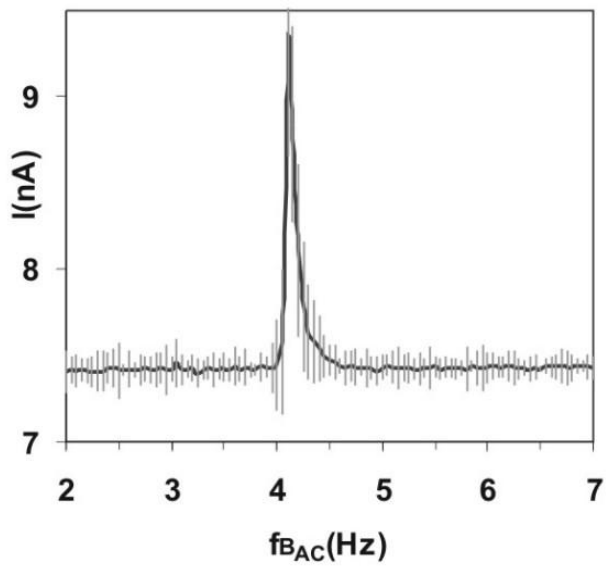

Fig. 2. Data taken by Pazur[18] illustrating the Zhadin effect[17]. A very weak AC magnetic field (40 nT) is applied to an aqueous solution of glutamic acid and the conductivity of the glu^+ ions is continuously monitored in terms of nA. The magnetic frequency in Hz is slowly ramped upwards. A sharp change in conductivity is observed at a frequency (4.25 Hz) close to the ion cyclotron resonance value for glu^+, (4.8 Hz).

The expression for the ICR resonant angular frequency is given as $w = (q/m)B_o$, where q and m are the charge and mass of the ion, and B_o the DC magnetic field. Confirmation that the charge-to-mass ratio was explicitly involved in this effect was obtained when isotopic $_{45}Ca$ was substituted for $_{40}Ca$ in a study on lymphocyte proliferation[25], showing that the frequency where the maximum ICR effect on proliferation occurred was shifted down by a factor of 12%, exactly what is to be expected for a change of mass of 5 parts out of 40.

Because these ICR effects appeared to violate simplistic analysis involving magnetic induction at first they evoked much suspicion in the scientific community. Many subsequent confirmations, however, performed on different model systems in diverse experimental situations , in part listed in Table 1, proved that these weak low-frequency effects are indeed real. It is clear that magnetic field combinations when tuned to ion cyclotron resonance, can act to regulate the flow of biological information, a conclusion that has important ramifications for electromagnetic medicine. Consider the following, from a recent review[26] of this subject:

The inescapable conclusion…is that the ICR mechanism, whatever its molecular basis, is of enormous biological significance. We are able to make reproducible and consistent physiological changes of various sorts in the widest imaginable range of genera simply by applying weak magnetic fields tuned to the charge-to-mass ratio of various biological ions. It is very clear that [this] must be part of a heretofore unknown system that carries physiological information/instructions, and that better understanding will open the way to providing a radically new means of controlling wellness.

In addition to medical applications already initiated using ICR techniques there are also a number of potential advances that are likely to be further developed in the future. Consider for example the observations found in a number of ICR studies that indicate merely changing the resonance condition from one ion to another will result in the opposite result. This phenomenon was first observed by S D Smith in his studies on diatom motility[6] and later reported by others[9,27-31] (Table 2). One explanation is that this effect likely reflects the endogenous nature of bioresonance, wherein multiple ion resonances are occurring simultaneously giving rise to a balanced physiologic outcome. If this is true then it should be possible in principle to selectively reduce the undesirable in favor of the desirable. There is evidence[32] indicating that ICR applications can increase the rates of proliferation in neuroblastoma cell culture. Is It possible that there exist yet-to-be-tried ICR conditions that would have the opposite effect, namely to reduce the rates of proliferation in cancer cell lines, thereby opening the way to new cancer fighting techniques?

MODEL SYSTEM	FREQ, Hz	B_o, mT	ION	RESPONSE
Diatom motility[6]	**16**	**20.9**	**Ca^{2+}**	**Motility✸**
	16	**41.0**	**K^+**	**Motility✸**
Embryonic bone[9]	**16**	**20.9**	**Ca^{2+}**	**Growth✸**
	16	**40.7**	**K^+**	**Growth✸**
Embryonic bone[27]	**16**	**20.9**	**Ca^{2+}**	**Growth✸**
	16	**40.7**	**K^+**	**Growth✸**
Plant growth[28,29]	**60**	**78.3**	**Ca^{2+}**	**Growth✸**
	60	**153.3**	**K^+**	**Growth✸**
Rat behavior [30]	**63**	**50**	**Mg^{2+}**	**More Active**
	38	**50**	**Ca^{2+}**	**More Passive**
Gravitropic response[31]	**35.8**	**46.5**	**Ca^{2+}**	**Up**
	54.7	**46.5**	**K^+**	**Down**

Table 2. Ionic tuning can drastically alter physiological outcome. Note that specific outcomes are observed for different magnetostatic fields at the same resonant frequency, or equivalently, for different frequencies at the same static magnetic intensity.

II. PRESENT CLINICAL ELECTROMAGNETIC PRACTICE

A number of diagnostic techniques based on electromagnetic principles, such as **Magnetic Resonance Imaging** (MRI), are universally accepted by physicians, to the point where objections are heard concerning the costs to the health care system because of overuse[33]. Neurologists universally use **Electromyography** (EMG) in their practice no less than **Electrocardiography** (EKG) is used by cardiologists and internists. It also should be understood that there are efficacious electromagnetic diagnostic tools that are used outside of the United States but not permitted in the US. The US Food and Drug Administration (FDA) oversee the introduction and use of medical devices with as much zeal as it supervises pharmaceuticals. The prospect of very expensive and time-consuming procedures for new devices tends to discourage the introduction of foreign devices, regardless of their efficacy and safety. This applies to both diagnostic and therapeutic devices.

One example of a foreign diagnostic device that is presently in clinical trials in the US is the Tissue Resonance Interferometer (**TrimProbe)**[34], invented by Clarbruno Vedruccio. Following its original use as an electromagnetic device for the remote detection of land mines and for airport screening, he discovered that microwave signals in the range 400 to 1350 MHz reflect differently from cancers as compared with healthy tissue. A hand-held non-invasive probe measures the degree of interference between the incoming and reflected signals, providing instant determinative results. It has been highly successful in prostate diagnosis, proving effective in distinguishing malignancies from prostate hyperplasia and prostatitis. This technique has also been used to detect bladder cancer. Because of its non-invasiveness, its speedy application and rapid diagnosis, all within a matter of minutes, this device has great potential as a tool for screening populations at risk.

It is clearly the case that the highly specific electrical nature of the nervous system should predispose it to exogenous electrical influence. This is shown in the great variety of electric medical procedures[35] presently in use as neurotherapies. Devices such as heart pacemakers and defibrillators are so widely known that they need no description. **Vagal nerve stimulation** (VNS) is widely used as an anti-convulsant therapy. **Deep brain stimulation** (DBS) uses

electrodes in the brain to treat Parkinson's disease and other movement disorders. Chronic pain is treated using the non-invasive **Transcutaneous electrical nerve stimulator** (TENS) directly on the back or the **Cranial electrothermal stimulator** (CES) on the head. Insomnia is treated with **Low-energy emission therapy** (LEET) using an electrode positioned in the mouth. In general these devices are employed as surrogates for already existing physiological endogenous mechanisms that require a boost or improvement, with the cardiac pacemaker serving to regulate the timing of heart contractions as an illustrative example. Presently there is an extension of this concept, with widespread ongoing research aimed at mimicking the electric signals needed to restore eyesight and muscle function that may have been lost because of disease or accident.

Less well known are a number of medical accepted EM therapies that are sufficiently energetic to be acknowledged as based either on Faraday induction or Joule heating. **Transcranial Magnetic Stimulation** (rTMS)[36,37] is used to treat depression. In this procedure, approved by the FDA as efficacious and safe, a large pulsed current is sent through a coil placed strategically over the head, thereby inducing a current through the brain. In part, this serves as a modern alternative to the much older (1938) use of applied currents to treat depression, namely **ElectroConvulsive Therapy** (ECT), wherein pulses or sinusoidal voltages are applied to the scalp through electrodes, producing power levels of several hundreds of watts directly into the brain.

Another purely inductive device, **Pulsed Magnetic Field** therapy (PMF), has found great success in treating bony nonunions, a rather common problem in which fractures do not knit properly. This device was introduced by Bassett and Pilla[38] following a long history showing that living bone enjoys remarkable electric properties[39] that can be used to advantage in growth and repair processes[40]. In a very real sense, the PMF work on bone in the 1970s was the springboard for the development 25 years later of rTMS.

Electromagnetically-induced hyperthermia (**Oncotherm**)[41] and **Electrochemical Treatment** (EChT)[42] have both been found useful in treating late-stage cancers, the former mostly in Europe and Asia, and the latter in China. The Oncotherm device applies carefully directed radiofrequency devices to tumor sites, slightly elevating the local temperature, which has the

interesting effect of killing off cancer cells without affecting healthy tissues. Neither procedure has as yet been approved by the FDA.

A much older device, dating back to the 1930s, **Diapulse**, applies radiant Joule heat deep into tissues. Because this device was introduced prior to the establishment of the FDA, its acceptance was ”grandfathered”, that is, allowed to be advertised and marketed on the basis of earlier widespread use. Electromagnetic energy is directed to specific areas of the body in the form of 600 pulses/s with each pulse lasting 65 ms. Although it was originally used to provide pain relief the extent of the therapeutic claims now includes “neurologically associated problems”. Along with a number of other devices making therapeutic claims related to radiofrequency use, the prominent frequency employed was 27.15 MHz, which has no special biological qualities, but is merely a frequency of choice permitted by the Federal Communications Commission (FCC).

This 27.15 MHz frequency has also appeared as the carrier wave in a similar arrangement to that used in the LEET insomnia device mentioned above, where one electrode is again placed in the mouth, in this case to treat cancer[43]. A much lower frequency, in the tens of Hz, modulates the 27.25 MHZ carrier. Presumably this ELF component represents the active anti-oncogenic component in this device.

Even higher frequencies, at 50 GHz and larger have also been reported as therapeutic aides. These devices, generally described as **Microwave Relaxation Therapy** (MRT)[44] machines are widely used in Russia and the Ukraine for mood behavior, and (anecdotally) to strengthen the immune system.

The author has previously attempted[45] to characterize neuroelectromagnetic therapies as falling into three categories: **subtle, gross, and disruptive**. The procedures of rTMS and ECT can be regarded as **disruptive**, considering that seizures have been associated with both, either deliberately or by accident. Similarly **gross** neurotherapies properly describe the great number of neural stimulators in use today. The term **subtle** is meant to convey the great difficulty in understanding how vanishingly small electric and magnetic signals are able to affect biological

systems. It is abundantly clear that such signals cannot be the result of either Faraday induction of voltage or thermal changes due to Joule heating.

III. NON-INDUCTIVE NON-THERMAL MEDICAL APPLICATIONS

The question of subtle electromagnetic effects in biology is not new. Observations indicating that minutely small electric currents, at levels far weaker than allowed by simple energetic estimates, are capable of profound biological effects. These were first reported in connection with living bone. Electret applications[46], likely supplying no more than a few hundred nanoAmperes, were found to significantly affect growth rates in bone. This fact was subsequently used in a number of orthopedic devices operating at 1-2 mA to repair bony non-unions[47]. The great advantage of the PMF techniques mentioned above was that currents at this level could be introduced at the repair site in a completely non-invasive way.

More recently, the FDA-approved application of ion cyclotron resonance magnetic fields to the problem of bone repair[48] has all but replaced the use of both weak electric currents and PMF pulses. Magnetic fields from a portable coil tuned jointly to Ca^{2+} and Mg^{2+} are applied for 30 minutes a day over a period of weeks. It should be emphasized that the efficacy of this application, achieving repair rates of 70% or more, remains unexplained, except insofar as one considers ion cyclotron resonance phenomena as empirically factual.

Adey also recognized the fact that such signals caused effects that were not readily explained. In attempting to understand results obtained in his laboratory showing a distinctly nonlinear response in connection with the calcium-efflux experiments, he suggested that low-energy transmission occurs at cell membranes by means of solitonic waves[49].

The results listed in Table 1 for effects related to ELF magnetic fields have their counterparts in experiments conducted with AC electric fields. In some ways these are unexpected. Unlike the transparency of biological matter to low-frequency magnetic fields polarization effects in the extracellular medium and the large electric field at the cell membrane make it difficult to apply AC electric fields to cells. Some of the weak AC electric-field clinical approaches involve the

use of invasive electrodes. Nonetheless these are noteworthy, considering the poor prognoses attached to illnesses such as glioblastoma.

Thus, one recent very promising therapy entails the use of electric fields at frequencies equal to or less than hundreds of kHz (**Tumor-Treating Fields**, or TTF) to treat aggressive glioblastoma and lung cancer[50,51]. Low-intensity electric fields, on the order of 1-2 V/cm, are found to slow the proliferation of all cells, cancer cells included. This is particularly advantageous in the treatment of brain cancer, because healthy brain cells tend not to proliferate in any case. Therefore the application of such fields is effective in slowing the increases in cancer cell production while leaving healthy cells unaffected. A somewhat similar effect has been discovered, but for applications at 50 Hz instead of hundreds of kHz. In this approach[52], a weak applied AC electric field is also used to fight cancer, not by reducing the proliferation of cancer cells, but by reducing their resistance to multidrug chemotherapy.

It is important to point out that these findings on the effectiveness of AC electric fields on cancer cell proliferation help illuminate why possible similar results that might be obtained using magnetic fields are so interesting. For one thing, there are problems related to AC electric field polarization effects that add constraints on how the cells are stimulated. By contrast because of tissue transparency to ELF magnetic fields, their clinical use will not only always be non-invasive, but also capable of being applied in more general ways.

Comparable effects of the sort observed using AC electric fields have already been observed using weak ELF magnetic fields. A number of reports have found changes in cell proliferation[8], particularly in lymphocytes, as a result of weak magnetic field stimulation. Further, in direct contrast to the electric-field reduction in chemotherapeutic resistance Liburdy discovered[53] that the resistance of breast cancer cells to tamoxifen was increased using 60 Hz magnetic fields.

Two interesting reports by Novikov highlight the clinical potential of weak magnetic fields. In the first case[54] he found that Ehrlich ascites cancer in rats can be dramatically reduced through the use of combined, ostensibly cyclotron-resonance tuned magnetic fields. In the second case[55] he demonstrated that these fields can also be used to hydrolyze, that is, break down, polypeptides by merely tuning to the charge-to-mass ratios of the constituent amino acids. One obvious

clinical direction suggested by this work is to use this approach to break down the b-amyloid plaque protein associated with Alzheimer's disease. Experiments have indicated that this is indeed possible in animal models, but it is not yet clear if this plaque is a cause of this disease or simply one of its symptoms.

The last entry in Table 1 indicating that weak ELF magnetic fields can play an important role in stem cell applications[16] is particularly exciting. The most difficult aspect to treating heart failure is the inability of damaged heart muscle to regenerate, leading when possible to heart transplants. Stem cell regeneration of heart tissue is an obvious remedy to this problem but the results to date have in general been slow. This stalemate has been dramatically changed through the use of weak ICR magnetic fields. It was demonstrated that cardiac stem cells from humans when exposed for five days to ELF resonance fields tuned to Ca^{2+} enjoyed significantly greater proliferation and differentiation, perhaps paving the way for a minimally manipulative means of regenerating diseased hearts. Because of this result there is now heightened interest in the use of ELF magnetic fields to enhance the implementation of regenerative medicine and tissue engineering.

A very different approach to ICR medical therapy is found in the **Seqex** device[56] which applies an oscillating magnetic field to the patient's entire body while simultaneously taking advantage of the local parallel vertical component of the earth's magnetic field to achieve resonance. Its most celebrated use has been to treat the debilitating depression that often accompanies chemotherapy following cancer remediation[57], but there have also been numerous anecdotal reports claiming success in treating other diseases, for example multiple sclerosis. There is reason to believe that the efficacy of this device may be related to its dramatic effect on antioxidants. In addition to the fact that this device employs holistic application of the combined fields, it is unique in that the applied ICR frequency is not calculated from ionic charge-to-mass ratios, but is determined by first finding in a prior separate evaluation the specific frequency conditions that sharply alters the whole-body bioimpedance. Once determined this frequency information is stored on a "smart card" for future treatments on that patient. It is worth noting that the change in whole-body bioimpedance at resonance is consistent with the sharp changes in ionic conductivity that were observed by Zhadin and others. This device has not as yet been introduced into the United States for clinical evaluation.

IV. WELLNESS AND ILLNESS: THE ELECTROMAGNETIC PERSPECTIVE

The medical community continues to regard therapeutic regimens based on weak magnetic fields with great suspicion. This fact is best illustrated by contrasting the interest shown in the use of AC electric fields to treat cancer while similar results using magnetic fields have all but been ignored. We do not seek to diminish the potential importance of these electric field effects, but it is apparent that ELF magnetic field research is still thought of as too far outside the mainstream. One useful rationalization in trying to explain the AC electric field effects has been to implicate voltage-dependent ion channels as the key interaction site. This allows one to avoid the thorny question surrounding the intrinsic difficulty in the lack of penetration of AC electric fields into the cell. By contrast, even though there appears to be no such thing as magnetically responsive ion channels, ELF magnetic fields are not impeded by the large electric field of the cell membrane, reaching all compartments inside the cell equally.

One alternate view, when looking at electromagnetic effects, may be to regard a common parameter found in both the electric and magnetic cases, perhaps involving frequency or some function of frequency, as the key distinction. This has already been hinted at in connection with ICR biological interactions.

Recently the author and colleagues[26] advanced a radical new view of electromagnetic effects in biology, suggesting that these strange new electromagnetic interactions can be explained in terms of an endogenously available substrate resonantly coupled to biological ions that enables information transfer for purposes of regulation. In this approach the tweaking of biological systems with weakly energetic electromagnetic signals reveals an underlying order to organisms, one in which the electromagnetic is elevated above the biochemical.

However, even if this generalized concept of systemic electromagnetic wellness is correct, there still remains unexplained the molecular basis that might tell us why nanoAmpere currents can help initiate bone formation or why nanoTesla magnetic fields can hydrolyze proteins. These fully replicated observations are well outside the simplistic electrical engineering that is so often used to discuss such effects. For example, it is inappropriate to express this work in terms of

Specific Absorption Ratio (SAR), because a different yardstick is required. The low levels of power absorbed by the biological system are literally many orders of magnitude below the 1 Watt/kg prescribed as safe. We know that very low levels of electromagnetic can affect biological systems, but do not know how this happens. One clearly obvious truth yet to be generally accepted, yet of vital importance to everyone, is that these effects are profoundly quantum mechanical in nature[17-21], and have little connection to the traditional safety limitations imposed by electrical engineers.

V. CONCLUSIONS

There can be little doubt that weakly energetic electromagnetic fields are biologically interactive to the point where they can be usefully applied in medically relevant therapeutic procedures. Not only does this fact suggest a bright future for the role of electromagnetism in medicine, but it also underscores the need to be very cautious when examining the effects of low-level electromagnetic fields on people. This conclusion, slightly rephrased, was expressed by the author when he wrote[58]:

> ***In the long run, [weak-field exposures for medical purposes] may be the only way to prove the case for biological plausibility among those who presently choose to deny that weak field low frequency magnetic fields do indeed interact with biological systems.***

VI. REFERENCES

1. Flexner A, 1910. Medical education in the United States and Canada. A report to the Carnegie Foundation for the Advancement of Teaching, New York. Carnegie Foundation for the Advancement of Teaching .
2. Cooke M, Irby D M, Sullivan W, and Ludmerer K M, 2006. American medical education 100 years after the Flexner Report. New Eng J Med 355: 1339-1344.
3. Liboff A R, Williams T Jr, Strong D M, and Wistar R Jr, 1984. Time-varying magnetic fields: effect on DNA synthesis. Science 223: 818-820.
4. Takahashi K, Kaneko I, Date M, and Fukada E, 1986. Effect of pulsing electromagnetic fields on DNA synthesis in mammalian cells in culture. Cell Mol Life Sci 42: 185-186.
5. Thomas J R, Schrot J, and Liboff A R, 1986. Low-intensity magnetic fields alter operant behavior in rats. Bioelectromagnetics 7: 349-357.
6. Smith S D, McLeod B R, Liboff A R, and Cooksey K E, 1987. Calcium cyclotron resonance and diatom motility. Bioelectromagnetics 8: 215-227.
7. Goodman R, and Henderson A S, 1988. Exposure of salivary gland cellsto low-frequency electromagnetic fields alters polypeptide synthesis. Proc Natl Acad Sci USA 85: 3928-3932.
8. Cossarizza A, Monti D, Bersani F, Cantini M, Cadossi R, Sacchi A, and Franceschi C, 1989. Extremely low frequency pulsed electromagnetic fields increase cell proliferation in lymphocytes from young and aged subjects. Biochem Biophy Res Comm 160: 692-698.
9. Smith S D, Liboff A R, and McLeod B R, 1991. Effects of resonant magnetic fields on chick femoral development in vitro. J Bioelect 10: 81-89.
10. Smith S D, Liboff A R, McLeod B R, and Barr E J. 1992. Effects of ion resonance tuned magnetic fields on N-18 neuroblastoma cells. In M.J. Allen M J, Cleary S F, Sowers A E, and Shillady D D, Eds, Charge and Field Effects in Biosystems-3, Birkhauser, Boston.
11. Fitzsimmons R J, Ryaby J T, Mohan S, Magee F P, and Baylink D G, 1995. Combined magnetic fields increase insulin-like growth factor II in TE-85 human osteosarcoma bone cell cultures. Endocrinology 136: 3100-3106.
12. Jenrow K A, Smith C, and Liboff A R, 1995. Weak ELF fields and regeneration in the planarian Dugesia tigris. Bioelectromagnetics 16: 106-112.
13. Prato F S, Kavaliers M, Carson J J, 1996. Behavioral evidence that magnetic field effects in the land snail, Cepaea nemoralis, might not depend on magnetite or induced electric currents. Bioelectromagnetics. 17:123-30.
14. Vorobyov V V, Sosunov E A, Kukushkin N I, and Lednev V V, 1998. Weak combined magnetic field affects basic and morphine-induced rat's EEG. Brain Res 781: 182-187.
15. Galland P, and Pazur A, 2005. Magnetoreception in plants. J Plant Res 118: 371-389.
16. Gaetani R, Ledda, M, Barile L, Cimenti, I., De Carlo F, Forte E., Ionta V, Giuliani L, D'Emilia, E, Frati G, Mirali F, Pozzi D, Messina E, Grimaldi S, Giacomello A, and

Lisi A, 2009. Differentiation of human adult cardiac stem cells exposed to extremely low-frequency electromagnetic field. Cardiovasc Res 82: 411-420.
17. Zhadin M N, Novikov V V, Barnes F S, and Pergola N F, 1998. Combined action of static and alternating magnetic fields on ionic current in aqueous glutamic acid solutions. Bioelectromagnetics 19: 41-45.
18. Pazur A, 2004. Characterization of weak magnetic field effects in an aqueous glutamic acid solution by nonlinear dielectric spectroscopy and voltammetry. Biomag Res and Tech 2: 8. doi: 10.1186/1477-044x-2-8.
19. Comisso N, Del Giudice E, De Ninno A, Fleischmann M, Giuliani L, Mengoli G, Merlo F, and Talpo G**,** 2006. Dynamics of the ion cyclotron resonance effect on amino acids adsorbed at the interfaces. Bioelectromagnetics 27**:**16-25.
20. Alberto D, Busso I, Crotti G, Gandini M, Garfagnini R, Giudice P, Gnesi I, Manta F, and Piragino G, 2008. Effects of static and low-frequency alternating magnetic fields on the ionic electrolytic currents of glutamic acid aqueous solution. Electromag Biol Med 27: 25-39.
21. Del Giudice E, Fleischmann M, Preparata G, and Talpo G, 2002. On the "unreasonable" effects of ELF magnetic fields upon a system of ions. Bioelectromagnetics 23: 522-530.
22. Liboff A R, 1985. Geomagnetic cyclotron resonance in living things. J Biol Physics 13: 99-102.
23. Blackman C F, Benane S G, Rabinowitz J R, House D E, and Joines W T, 1985. A role for the magnetic field in the radiation-induced efflux of calcium ions from brain tissue *in vitro*. Bioelectromagnetics 6: 327-337.
24. Bawin S M, Adey W R, and Sabbot I M, 1978. Ionic factors in release of 45Ca2+ from chicken cerebral tissue by electromagnetic fields. Proc Natl Acad Sci USA 75: 6314-6318.
25. Rozek R J, Sherman M L, Liboff A R, McLeod B R, and Smith S D, 1987. Nifedipine is an antagonist to cyclotron resonance enhancement of 45Ca incorporation in human lymphocytes. Cell Calcium 8: 413-427.
26. Foletti A, Grimaldi S, and Liboff A R, 2012. Electromagnetic medicine: The role of resonance signaling. Electromag Biol Med (in press).
27. Regling C, Brueckner C, Liboff A R, and Kimura J H, 2002. Evidence for ICR magnetic field effects on cartilage and bone development in embryonic chick bone explants (abstract) , 48th Ann mtg, Orthopedic Res Soc, Dallas.
28. Smith S D, McLeod B R, and Liboff A R, 1993. Effects of CR-tuned 60 Hz magnetic fields on sprouting and early growth of *raphanus sativus*. Bioelectrochem and Bioenergetics 32: 67-76.
29. Smith S D, McLeod B R, and Liboff A R, 1995. Testing the ion cyclotron resonance theory of electromagnetic field interaction with odd and even harmonic tuning for cations. Bioelectrochem and Bioenergetics 38: 161-167.
30. Zhadin M N, Deryugina O N, and Pisachenko T M, 1999. Influence of combined DC and AC magnetic fields on rat behavior. Bioelectromagnetics 20: 378-386.
31. Belova N A, and Lednev V V, 2000.Activation and inhibition of gravitropic response in plants by weak combined magnetic fields. Biophysics 45: 1069-1074.
32. Smith S D, Liboff A R, McLeod B R, and Barr E J. 1992. Effects of ion resonance tuned magnetic fields on N-18 neuroblastoma cells. In M.J. Allen, S.F. Cleary, A.E.

Sowers, and D.D. Shillady, Eds, Charge and Field Effects in Biosystems-3, Birkhauser, Boston.
33. Saslow L, Aug. 7, 1994. The boom in M.R.I.s: concerns grow on costs and overuse. N Y Times.
34. Gervino G, Autino E, Kolomoets E, Leucci G, and Balma M, 2007. Diagnosis of bladder cancer at 465 MHz. Electrom Biol Med 26: 119-134.
35. Liboff A R, and Jenrow, K A, 2002. Physical mechanisms in neuroelectromagnetic therapies. Neurorehabilitation 17: 9-22.
36. Barker AT, Jalinous R, and Freeston IL, 1985. Non-invasive magnetic stimulation of human motor cortex. The Lancet 325: 1106–1107.
37. George M S, Wasserman E M, Williams W A, Callahan A, Ketter T A, Basser P, Hallett M, and Post R M, 1995. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 2: 1853-1856.
38. Bassett C A L, Pawluk R J, and Pilla A A, 1974. Augmentation of bone repair by inductively coupled electromagnetic field. Science 184: 575-579.
39. Fukada E, and Yasuda I, 1957. On the piezoelectric effect of bone. J Phys Soc Japan 12: 1158-1162.
40. Bassett C A L, 1993. Beneficial effects of electro-magnetic fields. J Cell Biochem 51: 387-393.
41. Andocs G, Szasz O, and Szasz A, 2009. Oncothermia treatment of cancer: from the laboratory to the clinic. Electromag Biol Med 28: 148-165.
42. Chou C-K, McDougall J A, Ahn C, and Vora N, 1997. Electrochemical treatment of mouse and rat fibrosarcomas with direct current. Bioelecromagnetics 18: 14-24.
43. Costa F P, de Oliveira A C, Meirelles R, Machado M C C, Zanesco T, Surjan R, Chamms M C, de Souza Rocha M, Morgan D, Cantor A, Zimmerman J, Brezovich I, Kuster N, Barbault A, and Pasche B, 2011. Treatment of advanced hepatocellular carcinoma with very low levels of amplitude-modulated electromagnetic fields. Brit J of Cancer 105: 640–648.
44. Devyatkov N D, 1973. Influence of the millimeter wavelength range of electromagnetic radiation upon biological objects. Soviet Physics Uspekhi 110: 452-454 (in Russian).
45. Jenrow K A, and Liboff A R, 2004. Electromagnetic techniques in neural therapy. Chap. 14, Rosch P, and Markov M. (Eds) Bioelectromagnetic Medicine, Dekker, NY.
46. Fukada E, Takamatsu, T and Yasuda I, 1975. Callus formation by electret. Japan J Appl Physiol 14: 12.
47. Lavine L, Lustrin I, Shamos M H, Rinaldi R A, and Liboff A R, 1972. Electric enhancement of bone healing. Science 175: 1118-1121.
48. Diebert M C, McLeod B R, Smith S D, and Liboff A R, 1994. Ion resonance electromagnetic field stimulation of fracture healing in rabbits with a fibular ostectomy. J Orthop Res 12: 878-885.
49. Adey W R, 1993. Biologic Effects of Electromagnetic Fields. J Cell Biochem 4: 410-416.
50. Kirson E D, Dbaly V, Tovarys F, Vymazal J, Soustiel J F, Itzhaki A, Mordechovich D, Steinberg-Shapira S, Gurvich Z, Schneiderman R, Wasserman Y, Salzberg M,

Ryffel B, Goldsher D, Dekel E, Palti Y, 2007. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci USA 104: 10152-10157.

51. Kirson E D, Giladi M, Gurvich Z, Itzhaki A, Mordechovich D, Schneiderman R S, Wasserman Y, Ryffel B, Goldsher D, Palti Y, 2009. Alternating electric fields (TT fields) inhibit metastatic spread of solid tumors to the lungs. Clin Exp Metastasis 26: 633-640.
52. Janigro D, Perju C, Fazio V, Halkene K, Dini G, Agarwal M K, and Cucullo L, 2006. Alternating electrical stimulation enhanced chemotherapy: a novel strategy to bypass multidrug resistance in tumor cells. BMC Cancer doi: 10.1186/1471-2407-6-72.
53. Harland J D, and Liburdy,R P, 1997. Environmental magnetic fields inhibit the antiproliferative action of tamoxifen and melatonin in a human breast cancer cell line. Bioelectromagnetics 18: 565-562.
54. Novikov V V, Novikov G V, and Fesenko E E, 2009. Effect of weak combined static and extremely-low-frequency alternating magnetic fields on tumor growth in mice inoculated with the Ehrlich ascites carcinoma. Bioelectromagnetics 30: 343-351.
55. Bobkova N V, Novikov V V, Mevinskaya N I, and Fesenko E E, 2005. Reduction in the b-amyloid level in the brain under the action of weak combined magnetic fields in a model of Sporadic Alzheimer's disease. Biophysics 540: 52-57.
56. Liboff A R, 2007. Local and holistic electromagnetic therapies. Electromag Biol Med 26: 315-325.
57. Rossi E W, Corsetti M T, Sukkar S, and Poggi C, 2007. Extremely low frequency electromagnetic fields prevent chemotherapy induced myeloyoxicity. Electromag Biol Med 26: 277-281.
58. Liboff A R, 2010. Weak low-frequency electromagnetic fields are biologically interactive. European J Oncology 5: 51-62.

SECTION 18

Electromagnetic Field Exposure Effects (ELF-EMF and RFR) on Fertility and Reproduction

Prof. Jitendra Behari, PhD
Bioelectromagnetics Laboratory
School of Environmental Sciences
Jawaharlal Nehru University
New Delhi, India

Dr. Paulraj Rajamani, PhD
Bioelectromagnetics Laboratory
School of Environmental Sciences
Jawaharlal Nehru University
New Delhi, India

Prepared for the BioInitiative Working Group
November 2012

I. INTRODUCTION

Electromagnetic fields and radiofrequency radiation (RFR) interact with human tissues and may have adverse effects on fertility and reproduction. This review presents evidence for ELF-EMF and RFR effects on many parameters of male sperm function; leading to questions about the genotoxicity and carcinogenicity of such exposures on fertility and reproduction in men. Much of the evidence comes from human and animal studies on sperm and male fertility factors, but there are also studies showing adverse effects on fertility and miscarriage in women.

During the last four decades or so there has been a growing concern on the effects of electromagnetic radiations on biological systems in general. This is because of the global introduction of electronic devices on a massive level for communications and data transmission, personal wireless devices, air surveillance systems, industry applications, medical/diagnostic and therapeutic purposes that are now new sources of electromagnetic fields (ELF-EMF) and radiofrequency microwave radiation (RFR). This has added another layer of pollutant (electropollution) to a growing list of environmental contaminants in air, water, soil and from noise pollution which can adversely affect human health.

There are many sources of EMF in our environment and this non-ionizing radiation interacts with the human body. Use of electronic household items and cell phones are reported to decrease fertility potential in men by decreasing sperm count, motility, viability, inducing pathological changes in sperm and testes morphology, and so on (Erogul et al. 2006). In accordance with this, several authors (Agarwal et al. 2008, 2009; Kumar et al. 2010, 2011a; Pourlis 2009; Kesari et al. 2010, 2011, 2012) focused mainly on the male reproduction patterns. It involves the development from undifferentiated diploid stem cells to highly differentiated haploid stem cells. Spermatogenesis is a complex process and it is influenced by many genes and hormones. It takes place in the testis, which may be exposed to various microwave frequencies which are currently in use (Behari and Kesari 2006). Among various factors of infertility, oxidative stress has become the main focus of interest as a potential cause of male infertility (Agarwal and Said 2003; Aitken and Roman, 2008; Kumar et al, 2010, 2011a). Male infertility is commonly associated with high rates of DNA (deoxyribonucleic acid) damage in the spermatozoa and such damage is correlated with a wide range of adverse clinical outcomes. Several studies, especially at power frequency 50/60

Hz magnetic field have found an association of exposure to human health, with emphasis on a range of clinical conditions including childhood leukaemia, brain tumours, genotoxicity and neurodegenerative disease, infertility, birth defects, increased risk of miscarriage, childhood morbidity and de novo mutations (Hardell and Sage 2008; Gharagozloo and Aitken 2011; Garcia et al. 2008; Huss et al. 2008; O'Carroll and Henshaw 2008; International Agency for Research on Cancer (IARC) Monographs of the Evaluation of Carcinogenic Risks to Human 2002; California Health Department Services (CHDS) Report 2002). Sperm DNA damage is therefore regarded as a potential risk factor to the development of normal human embryos leading to impaired embryonic development.

II. THE BIOPHYSICS OF EXTREMELY LOW FREQUENCY FIELDS

Whenever a body having finite conductivity (biological body) is intercepted by EMF it induces electric fields and circulating electric currents, which in turn competes with endogenous current and voltages, thus disturbing normal physiological balance. The depth of penetration within the body depends upon its frequency and the electric properties of the exposed portion in the body. If the current density exceeds a certain threshold value, excitation of muscles and nerves due to membrane depolarization is possible. The mode of interaction of non-ionizing radiation with biological systems can be broadly divided into two parts: extremely low frequency and radiofrequency/microwaves.

Whenever an electric field interacts with a biological body the incident field will be distorted, such that the external field will be nearly perpendicular to the boundary surface. At 60 Hz

$$E_{internal} / E_{external} \approx 4(10^{-8}). \quad (1)$$

Thus a 60 Hz external field of 100 kV/m will produce an average internal E field of the order of 4mV/m.

As far as the magnetic components of the extremely low frequency fields are concerned, magnetic permeability μ of most biological materials is practically equal to that of free space $(4\pi.10^{-7})$ H/m. This signifies that ELF H field 'inside' will be practically equal to the H field 'outside'. Only exceptions could be those biological materials that have magnetic particles inside. A time varying magnetic field (also electric field) can also induce electric currents into stationary conducting objects. Thus, all modes of interaction of time varying E fields with living matter may be triggered by time-varying (not by static) magnetic field. According to Faraday's law of electromagnetic induction time varying magnetic flux will induce E fields with resulting electrical potential differences and "eddy" currents through available

conducting paths. Sources generating low frequency electric and magnetic fields are more likely to produce physiologically significant internal E fields through the mechanism of magnetic induction. If an erect person is targeted by a vertical electric field it will be considerably "enhanced" at the top of the person's head and shoulder, and one would predict therefore that the field in the tissue would also be enhanced above that of a flat slice exposed to the same field (Deon, 1982). In a 60 Hz electric field of 1kV/m in air, the current densities (Am/m^2) in neck, waist and ankle turn out to be $0.591x10^{-3,}$ $0.427\ x^{-3}$ and $3.35x10^{-3}$ respectively (Polk 1986).

III. THE BIOPHYSICS OF RADIOFREQUENCY AND MICROWAVE FIELDS

The biological bodies are inhomogeneous, having tissue-specific dielectric properties and the complexity of the shape; which make the computations of the induced field difficult. The fields induced inside the body act differently depending upon the frequency and more particularly on (L/λ), (where L is the length of the biological body and λ the wavelength of the incident field) upon, but are not limited to the following parameters:

(i) The location of the field with respect to the surroundings, e.g. if there are metallic objects around, the person is grounded or otherwise.

(ii) Polarisation of the incident wave with respect to the orientation of the human body.

(iii) Size of the human body (L) with respect to the wavelength (λ) of the incident radiations (L/λ).

(iv) The portion of the human body.

(v) The electrical properties of the tissue in question.

In free space propagation of electromagnetic field the power density is given by

$$\text{Power density} = E^2/1200\,\Pi \ \text{mW/cm}^2 \qquad (1)$$

Where, E is the electric field strength.

The frequency in the radio frequency-microwave region are somewhat penetrated inside the biological body interacting with the tissues inside.

From simple biophysical considerations, it follows that each body has a characteristic resonant frequency depending upon the length of the long axis. Correspondingly, for the same level of incident exposure the average value of power absorbed is dependent upon the length of the body, the degree of decoupling decreasing the average value of SAR by more than an order of magnitude. It is suggestive that absorbed RF energy can be converted into other form of energy and can cause interference with the functioning of the biological systems. A significant portion of this energy is converted into heat (absorption). The biological effects are frequency dependent. Well below 100 KHz, the induced fields can even stimulate nervous tissue.

IV. FERTILITY AND REPRODUCTION EFFECTS: ELF-EMF FIELD EXPOSURE

Since the biological body is diamagnetic it is transparent to the static magnetic field. It can therefore interact with the motional activity of paramagnetic materials. Amara et al (2006) has shown that adult male rats exposed to such fields (128 mT, 1hr/day for 30 days) show a decrease in testosterone levels and induced DNA oxidation. Subchronic exposure failed to alter spermatogenesis in rat testis. In a similar study Hong et al (2005) also concluded that 50 Hz EMFs (0.2 mT or 6.4 mT, exposed for a period of 4 weeks) may have the potential to induce DNA strand breakage in testicular cells and sperm chromatin condensation in mice.

Al-Akhras et al (2006) also treated male adult rats to 50 Hz sinusoidal magnetic field (25μT or 250 mg) for 18 consecutive weeks. They reported no significant effects on the absolute body weight and the weight of the testis of the exposed rats. However the weight of the seminal vesicles and preputial glands were significantly reduced in the exposed male rats, along with significant reduction in sperm count of the exposed rats. There was no significant effect on the serum levels of male follicle stimulating hormone (FSH) during the 18 weeks of exposure period. On the other hand there was a significant increase in the serum levels of male luteinizing hormone (LH) after 18 weeks of exposure ($p<0.005$) while testosterone levels were significantly decreased after 18 weeks of exposure period. These results suggest that long term exposure of ELF could have adverse effects on mammalian fertility and reproduction.

Different results have been presented by Chung et al (2005) where animals exposed in-utero and subsequent neonatal exposure to a 60 Hz EMF(field strength 500 μT or 5000 mG) from

day 6 of gestation to day 21 of lactation, did not produce any detectable alteration in offspring spermatogenesis and fertility.

Akdag et al (2006) examined the effects of ELF magnetic fields (1.35 mT) on sperm count, malondialdehyde concentration, the histology of organs as: testes, brain, liver, and kidney tissues, p53 immunoreactivity of bone marrow and the serum concentrations of Cu^{2+}, Zn^{2+},Mn^{2+} and Fe^{3+} in rats. These authors found no statistically significant alteration except in Mn^{2+} concentrations ($p<0.001$).

Influence of ultrasound (frequency 2,4 and 8 MHz) and constant magnetic field (7T) on gametes, zygotes and embryos of the sea urchin were studied by Drozdov et al (2008). Magnetic field exposure interrupts the process of the gamete fusion but did not influence gametes, embryos, or embryonic development. The nature of these two stimuli is of different type. Ultrasound may heat up the water if is of sufficient power, by way of increase in water temperature and cavitation temperature, which may also break the cellular structure. The effect of magnetic field is connected to the response of the cortical cytoskeleton, which consists of bundles of actin microfilaments. The rearrangement of the cortical cytoskeleton occurs during the first 20 minutes after the contact of sperm with the egg.

Kim et al (2009) examined the effect of a 16-week continuous exposure to ELF magnetic field (MF) of 14 or 200 μT (140 or 2000 mG) on testicular germ cell apoptosis in mice. They reported no significant adverse effects of MF on body weight and testosterone levels in mice. In TUNEL staining (in situ terminal deoxynucleotidyl transferase-mediated deoxy-UTP nick end labelling), germ cells show a significantly higher apoptotic rate in exposed mice than in sham controls ($P<0.001$). TUNEL-positive cells were mainly spermatogonia. In an electron microscope study, degenerating spermatogonia showed condensation of nuclear chromatin similar to apoptosis. These results indicate that apoptosis may be induced in spermatogenic cells in mice by continuous exposure to 60 Hz of 14 MF μT (140 mG).

Roychoudhury et al (2009) examined the effects of 50 Hz extremely low frequency electromagnetic field on in vitro rabbit spermatozoa motility. These authors also studied the effects after insemination. Pooled semen samples and a control were exposed to 50 Hz ELF EMF. The difference of the test groups G1 and G2 with the control group CG (75.56%) for spermatozoa motility were found to be significant ($P<0.01$). Differences were significant ($P<0.01$) for curvilinear velocity (VCL) between the test group G3 (122.38 μ/s). Hormonally simulated adult (9-12 months) females (n=140) were inseminated with semen samples from G1, G2, G3 and G4 (0.88×10^9 spermatozoa /0.5 ml average insemination portion)

immediately after ELF EMF exposure and fertilization (kindling) rates were calculated. For the G2 it was 54.28% data indicate 50 Hz ELF EMF induced alterations of spermatozoa motility and kindling rate in rabbits, therefore influencing fertility.

Cao et al (2009) also reported that magnetic fields at 1000 Hz or 2000 Hz may damage the testis by inducing injury to seminiferous tubules and Leydig cells, thickening the basal membrane, derangement, exfoliation, massive apoptosis and necrosis of spermatogenic cells in the lumen, epididymis, and consequently result in the absence of sperm.

Bernabo et al (2010) assessed the effect of acute (1hr) exposure of boar spermatozoa to an extremely low frequency electromagnetic field (ELF-EMF) (50 Hz, MF 0-2 mT) on early fertility outcome. They examined morpho-functional integrity of capacitated spermatozoa in vitro and reported in vitro ELF-EMF >0.5 mT induced a progressive acrosome damage, thus compromising the ability of spermatozoa to undergo acrosomal reaction after zona-pellucida stimulation and reducing the in vitro fertilization outcome. These effects became evident at 0.75 mT and reached the plateau at 1 mT. Under in vivo conditions, ELF-EMF intensity of 1 mT was able to compromise sperm function, significantly reducing the fertilization rate. In addition, the exposure of oviducts field ≥0.75 mT in the absence of spermatozoa was able to negatively affect early embryo development. In fact it was found to cause a slowdown in the embryo cleavage. It is apparent that at mentioned intensities the fields has negative effect on early fertility outcome in a predictive animal model.

Earlier these authors (Bernabo et al 2007) reported that MF-ELF influence negatively by dramatically effecting sperm morphology and function.

The blood-testis barrier is sensitive to environmental stimulation, which can affect its permeability and then result in antisperm antibody (AsAb) generation, which is a key step in male immune fertility. Wang et al (2010) reported the results of male mice exposed to electromagnetic pulse (EMP) by measuring the expression of tight-junction of associated proteins(ZO-1 and Occludin), vimentin microfilaments, and mice were sham exposed or exposed to EMP at two different intensities (200 kV/m and 400 kV/m) for 200 pulses. The testes were collected at different points after EMP exposure. Immunofluorescence histochemistry, western blot, laser confocal microscopy and RT-PCR were used in this study. Compared with sham group, the expression of ZO-1 and TGF-beta3 were significantly decreased accompanied with unevenly stained vimentin microfilaments and increased serum AsAb levels in EMP-exposed mice. These results are indicative of a potential BTB injury and immune infertility in male mice exposed to certain intensity of EMP.

Lorio et al (2011) studied the functional relationship between the energy metabolism and the enhancement of human sperm motility induced by ELF-EMF was investigated. Sperm exposure to ELF-EMF resulted in a progressive and significant increase of mitochondrial membrane potential and levels of ATP, ADP, and NAD(+) associated with sperm kinetic parameters. However no significant effects were detected on other parameters such as ATP/ADP ratio and energy change. When carbamoyl cyanide m-chlorophenyllhydrazone (CICCP) was applied to inhibit the oxidative phosphorylation in the mitochondria, the values of energy parameters and motility in the sperm incubated in the presence of glucose and exposed ELF-EMF did not change, thus indicating that the glycolysis was not involved in mediating ELF-EMF stimulatory effect on motility. By contrast, when pyruvate and lactate were provided instead of glucose, the energy status and motility increased significantly in ELF-EMF-treated sperm. Under these culture conditions, the inhibition of glycolytic metabolism by 2-deoxy-D-glucose (DOG) again resulted in increased values of energy and kinematic parameters, indicating that gluconeogenesis was not involved in producing glucose for use in glycolysis. These authors concluded that the key role in mediating the stimulatory effects exerted by ELF-EMF on human sperm motility is played by mitochondrial oxidative phosphorylation rather than glycolysis. Earlier these authors (Lorio et al 2007) reported that ELF-EMF exposure can improve spermatozoa motility and that this effect depends on the field characteristics. ELF-EMF with 50 Hz and square wave shape (amplitude 5 mT),while that of a sine wave of the same amplitude (also of 2.5 mT) and the same frequency had no such effect. Further a three hour exposure in the first case had the effect on sperm motility persisting for 21 hours.

People connected to local area networks wirelessly (Wi-Fi) were examined for human spermatozoa. These authors (Avendano et al 2012) selected sperms from 29 healthy donors for their capability to swim. This study using a laptop as a source contributed both ELF-EMF and RFR to the exposure conditions. Each sperm suspension was divided into two aliquots. One sperm aliquot (experimental) from each patient was exposed to an internet connected lap top by Wi-Fi for 4 hours, whereas the second aliquot (unexposed) was used as control and incubated under identical conditions without being exposed to the laptop. These authors evaluated sperm motility, viability, and DNA. These authors reported that normozoospermic, exposed ex vivo during 4 hour to a wireless internet –connected laptop showed a significant decrease in progressive sperm motility and an increase in DNA fragmentation. Level of dead sperm showed no significant differences between the two groups. They concluded that the effect (which is non-thermal) decreased motility and induced DNA fragmentation. It is

therefore speculated that keeping a laptop connected wirelessly to the internet on the lap near the testes may result in decreased male fertility.

Sage et al (2007) reported that personal and occupational use of personal digital assistants (PDAs or palm-held wireless units) produce high intensity bursts of ELF-EMF exposure in persons that carry a PDA close to the body (i.e., in a pocket or in a belt); or held to the head for cell phone conversations. ELF-EMF emissions of 10μT (100 mG) were recorded on PDAs during normal office use over a 24 hr test period. Results of ELF-EMF measurements show that email transmit and receive functions produce rapid, short duration ELF-EMF spikes in the 2-10μT (20 to 100 mG) range, each lasting several seconds to over a minute, depending on the download size. Switching the PDAs produced continuously elevated ELF-EMF pulses of over 90 μT on two units. Thus the user who wears the PDA may be receiving high-intensity ELF-EMF pulses throughout the day and night.

Avendano et al (2012) investigated the effect of laptop computers connected to internet through Wi-Fi on human sperm motility. Donor sperm samples, mostly normozoospermic, exposed ex vivo during 4 hours connection showed a significant decrease in progressive sperm motility and an increase in sperm DNA fragmentation due to nonthermal effect, thus showing potential risks to male fertility.

Bellieni et al (2012) has investigated a much wider issue of reproduction relating to that of fetal growth and the effect of emissions from lap top computers (LTC). Such wireless and ELF-EMF exposures may have adverse effects on the offspring. They measured magnetic field in the range 1 Hz -400 kHz range as emitted from LTC. These field have the advantage that being quasi static can penetrate inside the body and thereby induce voltage and induce currents. The authors reported that the magnetic field at dominant frequencies ranged from 1.8-6 μT (18 to 60 mG), where from the power supply ranges from 0.7 to 29.5 μT (7 to 295 mG). They found that the power supply produces strong intracorporal electric current in the fetus and in the mother, higher than ICNIRP (1998) basic restriction recommend to prevent adverse health effects. The field emissions from video terminals are reported to be low (0.1μT or 1 mG) and the effect of higher exposures needs to be investigated (Bellieni et al 2012)

Sun et al. (2005) investigated the effects of EMR emitted by computers on human sperm quality and did not find any adverse effect.
An observation that women who use video display terminals suffers miscarriages has led to the beginning of diagnosing the possible adverse effects of electric and magnetic fields

Extremely low frequency electromagnetic fields are likely to produce greater damage to the body systems for several reasons. One that these frequencies are close to those of physiological range and hence any overlap of these can perturb on-going biological processes. When in close contact with the body the generation of eddy currents and accompanied heating are added parameters. To differentiate their respective contributions on biological system is an impossible demand.

Extremely low frequency EMF effects induced due to electric(E) blankets generate eddy currents in the body.60 Hz magnetic field exposure generate about 3-4 mG for waterbeds (W) and about 15 mG for E (Electric Blankets),as reported by (Wertheimer and Leeper 1986). They have estimated that electric fields are of the magnitude 100 V/m. E and W both have the potential for providing excessive body heating, which may have adverse effect on sperm (Van Demark and Free 1970), leading to adverse effect on the process of embryogenesis (Edwards et al 1974,Lacy et al 1981). This high temperature could also be teratogenic in humans too (Miller et al 1978, Fraser and Skelton 1978).It is obvious that either the heat or the electromagnetic fields produced by electric or bed heating might affect the fetus. These authors concluded that E or W use has a direct effect on fetal development. It is argued that heat or electromagnetic field exposure is he seasonal. Both prolonged gestation and fetal loss have been shown to be associated with high blanket settings used by the mother, but not those used by the father. Earlier workers have also pointed out that electromagnetic exposure may cause abnormal fetal development (Delgado et al 1982).Marx (1981) pointed out that current and field distribution in embryos, responsible for normal fetal development are disturbed due to the presence of externally imposed fields .

Li et al (1995) studied the effect of prenatal electromagnetic field exposure on the risk of congenital urinary tract anomalies (CUTAs) among women with a history of subfertility as well as in general population. These authors found no consistent relation between the risk of CUTAs and prenatal exposure to electromagnetic fields from E,W ,and video display terminals among all cases of controls. The risk appeared to increase with increasing duration of use and was greatest among women who used Es during the first trimester .CUTA cases

exposed to Es prenatally appeared more likely to have anomalies of the ureter, bladder than unexposed cases. However there is an absence of association with the risk of electrically heated water beds and video display terminals and demands further investigations. They further pointed out that only women with a history of subfertility were subject to said exposure ,since the positive association between potential E use and risk of CUTAs was observed in this group. They concluded that out of the three E,W and video terminals, E has the maximum capacity,keeping in view the proximity with all parts of the body and duration of exposure. Women with subfertility history are more prone to adverse pregnancy outcome.

Juutilainen et al (1993) carried out case control study, although on a small number ,on women .They measured magnetic field at the front door and reported a five-fold increase in preclinical miscarriage. Lee et al (2001) conducted a case control study nested in a miscarriage study. They defined cases as women who had a clinical miscarriage before 20 weeks of gestation and controls as women who had a live birth. They observed a gradient in miscarriage risk as the number of environmental parameters increased above the 50th percentile. Their findings are not consistent with the results of mechanistic and mammalian studies (Portiere and Wolfe 1987) ,while some laboratory results supports alterations in the development of chick embryos exposed to EMF.(Farrell et al 1997). While numerous data have been generated but are inconclusive and the possibility of more funding seems remote.

In summary the possibility of immediate abortion has not found favour with the researchers. However a weak link is possible. A temperature rise causing adverse effect on sperm is possible and certainly avoidance is recommended more so for pregnant women. Another point of interest would be to see if any adverse effects are reversible.

The area certainly demands more investigations.

A summary of these data is presented in Table 1 (Studies on Effects of ELF-EMF on Fertility and Reproduction).

Table 1: Table showing the overall Effect of Extremely Low frequency electromagnetic field effects on reproduction and fertility

Organism used	**Mode of exposure**	**Parameters studied**	**Conclusion**	**Reference**
Human sperm	internet-connected laptop by Wi-Fi for 4 hours	sperm motility and an DNA fragmentation	Decrease in motility and increase in DNA fragmentation	Avendano et al, 2012
Human sperm	ELF -EMF	Sperm kinematics	Increase in mitochondrial membrane potential	Lorio et al 2011
Mice	4h d 2 m at 3 mT EMF with Polygonum aviculare	Sperm motility and morphology	Motility affected. With *P. aviculare* is sperm quality increased	Milan et al. 2011
Boar spermatozoa	Acute (1h) 50 Hz ELF	Early embryo development	Reduction in fertilization rate, Affect embryo development	Bernabo et al. 2010.
NMRI mice (Naval Medical Research Institute)	50 Hz, 0.5 mT EMF 4 h for 2 weeks	Fertility and height of epithelial cells	Decrease in blastocyte and increase in the height of epithelial cells	Rajaei et al.2010
Rabbit spermatozoa	50 Hz ELF	Spermatozoa motility	Change in motility and kindling rate	Roychoudhury et al.2009
ICR mice	X- ray, 1000 Hz and 2000Hz	Sperm motility	Affect testis function	Cao et al. 2009
BALB/c mice	ELF 60 Hz ,0.1 or 0.5 mT 14 or 200 mT	Apoptosis	Induced apoptosis	Kim et al. 2009
Balb C mice	Electromagnetic pulse (EMP)	Tight-junction-associated proteins,transforming growth factor-beta and AsAb level in serum	Decrease in expression of protein	Wang et al 2010

Table 1 continued …

human spermatozoa	ELF-EMF 5 mT and frequency of 50 Hz.	sperm motility	Square waveform of 5 mT amplitude and frequency of 50 Hz increase sperm motility.No change in 5 mT sine wave (50 Hz) and a 2.5 mT square wave (50 Hz	Lorio et al 2007
Sprague – Dawley rat	ELF 2hour for 2 months	Sperm count, histology, p53 immunoreactivity of bone marrow	No adverse effect. Increase in Mn2+.	Akdag et al 2006
Rat	static magnetic field (SMF) and cadmium	Antioxidant enzymes activity	SMF with Cd disrupt antioxidant response	Amara et al 2006
Mice	50 Hz .02,3.2or 6.4 mT for 2 weeks or 4 weeks	Testicular histology, weight quantity and motility of sperm	Reduced testicular weight, decreased sperm motility. High rate of deformity in sperm	Hong et al 2003
Pregnant women	Case control study (Magnetic field)	Miscarriage	Miscarriage before 20 weeks of gestation	Lee et al 2001
Sperm	12.5, 25, 50 and 100 cGy X-rays	DNA damage	Increase in DNA migration	Singh and Stephens 1998
Pregnant women	Electric blanket, electric heated water bed, and video display terminal	Congenital urinary tract abnormality(CUTA)	Increased risk of CUTA	Li et al 1995
Human	Extremely low frequency EMF(60Hz)	Abortion rate, Fetal development	Excess abortion	Wertheimer and Leeper(1986)

V. FERTILITY AND REPRODUCTION EFFECTS REPORTED FOR RADIO-FREQUENCY AND MICROWAVE EXPOSURE

Nakamura et al. (2000) found that exposure to 2.45 GHz continuous wave (CW) microwave at 2mW/cm^2 power density for 90 min decreased uteroplacental blood flow, increased progesterone and $PGF_2\alpha$ in pregnant rats. Dasdag et al. (2003) reported the decrease in seminiferous tubule diameter in male rat testes after exposure. They used commercially available 890-915 MHz GSM (global signal module) with 0.141 W/kg whole body SAR. More recently, Aitken et al. (2005) found significant damage to mitochondrial and nuclear genome in epididymal spermatozoa of mice, when exposed to RF 900 MHz EMW, 12 hr a day for 7 days. Several authors (Fejes et al. 2005; Ji-Geng et al. 2007; Kesari and Behari, 2008) have also observed that carrying the mobile phones near reproductive organs for longer time may have negative effects on the sperm motility and male fertility.

Aitken et al (2005) exposed mice to 900 MHz radiofrequency electromagnetic radiation at a SAR of 90 mW/kg inside a waveguide for 7 days (12 hr/day). Following exposure DNA damage to caudal epididymal spermatozoa was assessed. These authors reported no gross evidence of single-or double strand DNA breakage in spermatozoa taken from treated animals. However an analysis of DNA integrity revealed significant damage to both the mitochondrial genome ($P<0.05$) and the nuclear beta-globin locus ($P<0.01$). This study suggests that while RF EMR does not have a dramatic impact on male germ cell development, a significant genotoxic effect on epididymal spermatozoa is seen.

Kilgalton and Simmons (2005) report decreased semen quality with prolonged use of cell phones with negative effects on sperm motility characteristics (Fejes et al, 2005). It has been shown that sperm DNA damage is not repaired, because of chromatin structure (Singh and Stephens 1998).

Yan et al (2007) studied the effects of cellular phone emissions on sperm motility in rats. Rats were exposed to two 3-hr periods of daily cellular phone emissions for 18 weeks, sperm samples were then collected for evaluation. These authors concluded that exposed group of

rats exhibited a significantly higher incidence of sperm cell death than control group rats. In addition, abnormal clumping of sperm cells was present in rats exposed to cellular phone emissions and absent from control group rats. A study carried out in Poland (Wdowiak et al 2007) on the population using mobile phone (GSM equipment), spread over a period (1-2 years) indicates sperm quality is lowered. The authors report a decrease in the percentage of sperm cells with normal motility in the semen. The decrease in motility correlates with the frequency of using mobile phones. These two finding seem to be mutually supportive.
However there are also reports indicating no effects (Panagopoulos and Margaritis 2008, 2009, 2010).

Overall, the evidence from various laboratories studying fertility and reproduction effects over the last ten years is important enough raise questions about possible public health consequences of chronic, long-term exposure to mobile phone use, and when carried on the body close to the reproductive organs. While assessing the biological implications of mobile phone radiofrequency exposures, field based experiments are not possible. Sham exposure controls cannot be obtained. Therefore it is imperative to fall back upon laboratory experiments performed in a variety of situations (e.g. animals at different distances from the mobile phone and head) while also simulated variable distances and angles for the mobile phone variation while in actual use.
Gutschi et al (2011) studied human sperm obtained from 2110 patients attending clinics from 1993 to 2007. Semen analysis was performed in all patients. Serum free testosterone (T), follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin (PRL) were collected from all patients. Information on cell phone use from each patient was collected and the subjects were divided into two groups according to their cell phone use. Group A: cell phone use (n=991), Group B: no use (n=1119). Patients with cell phone use showed a significant higher T and lower LH levels than those who did not use a cell phone. However no significant difference was observed regarding FSH and PRL values. These authors concluded that cell phone use had a negative effect on sperm quality in men.
Kesari et al (2011) assessed free radical formation due to mobile phone exposure (2 hr a day for 35 days) and examined fertility patterns in 70-days old male Wistar rats. The specific absorption rate of the mobile phone was 0.9 W/kg. An analysis of anti-oxidant enzymes glutathione peroxidise($p<0.001$) and superoxide dismutase ($p<o.007$) showed a decline, while

an increase in catalase ($p<0.005$) was observed. Malondialdehyde ($p< 0.003$) showed an increase and histone kinase ($p=0.006$) showed a significant decrease in the exposed group. Correspondingly, micronuclei also showed a significant decrease ($p<0.002$). A change in sperm cell cycle of G_0 –G_1 ($p=0.42$) and G_2/M ($p=0.022$) was recorded. These authors concluded that changes occurred due to overproduction of ROS and oxidative damage, leading to infertility.

Yan et al (2007) studied the effects of cellular phone emissions on sperm motility in rats. Rats were exposed to two 3-hr periods of daily cellular phone emissions for 18 weeks. After the exposure period, sperm samples were collected for evaluation. The authors concluded that exposed group of rats exhibited a significantly higher incidence of sperm cell death than control group rats. In addition, abnormal clumping of sperm cells was present in rats exposed to cellular phone emissions and absent from control group rats.

A related issue is the corresponding effect on male infertility.

Sommer et al (2009) undertook a very exhaustive study where male and female mice were chronically exposed (life-long, 24 hr/day) to mobile phone frequency EMF at 1966 MHz (UMTS). They studied their development and fertility patterns over four generations by investigating histological, physiological, behavioural and reproductive functions. They tested SAR from the time of mating at 0 (sham), 0.08, 0.4 and 1.3 W/kg. Power densities were kept constant for each group (0, 1.35, 6.8 and 22 W/m^2), resulting in varying SARs due to different number of adults and pups. The results show no harmful effects of exposure on the fertility and development of the animals. The number and the development of the pups were not affected by the exposure. These authors concluded no harmful effects occurred with long-term exposure of mice to UMTS mobile phone frequency radiation over several generations.

DeIuliis et al (2009) used purified human spermatozoa for exposure to electromagnetic radiation at 1.8 GHz with specific absorption rates varying from 0.4 to 2.75 W/kg. These investigators reported that motility and vitality were significantly reduced after RFR exposure, while the mitochondrial generation of reactive oxygen species and DNA fragmentation was significantly elevated ($P<0.001$). They also found a highly significant relationship between SAR, the oxidative DNA damage biomarker 8-OH-dG, and DNA fragmentation after exposure. These results have bearing on safety of people of reproductive age, and wellbeing of their offspring. Erogul et al (2006) also support these finding by showing effect on sperm motility and that long-term exposure may lead to behavioural or

structural changes of the male germ cell. These may appear later in life and need investigation on a longer term basis.

As a follow up of the above, Otitoloju et al (2010) exposed male mice to radiofrequency radiations at mobile phone (GSM) base station-level RFR. Sperm head abnormalities occurred in 39% to 46% of exposed mice, but in only 2% of the controls ($P<0.005$). The major abnormalities observed were knobbed hook, pin head and banana-shaped sperm head. The abnormalities were also found to be dose-dependent. This may have severe consequences for the off spring.

Gul et al (2009) investigated toxicity of microwaves (as emitted by cellular phones on ovaries in rats. In this study 82 female rats of aged 21 days (43 in the study group and 39 in the control group) were used. Pregnant rats exposed to mobile phones that were kept underneath the cages during the whole period of pregnancy. A mobile phone in a standby position for 11 hr and 45 min was turned on to speech position for 15 min every 12 hr and the battery was charged continuously. On the 21st day after the delivery , the female rat pups were killed and the right ovaries were removed. The volumes of the ovaries were measured and the number of follicles in every tenth section was counted. These authors found that the number of follicles in pups exposed to mobile phone microwaves suggest that intrauterine exposure has toxic effects on ovaries.

Salama et al (2010) examined the accumulating effects of exposure to electromagnetic radiation emitted by a conventional mobile phone (800 MHz, standby position, kept opposite to the testis) on the testicular function and structure. The animals were exposed 8 hr daily for a period of 12 weeks in a specially designed cage. Semen analysis and sperm function tests were conducted weekly. Other parameters examined were histological testicular sections and serum total testosterone. When compared with other two groups (stress control and ordinary), the exposed animals showed a drop in sperm concentration at week 6, which became significant at week 8. Mobile sperm population showed similarity amongst the three study groups until week 10 when it declined significantly, and thereafter in phone and stress control groups, with more significant decline in the exposed animals (50.6% and 72.4%, respectively). Histological examination showed a significant decrease in the diameter of seminiferous tubules in the exposed group vs the stress and ordinary controls (191 μm vs. 206 and 226 μm, respectively). The authors concluded that the pulsed radiofrequency emitted by a conventional mobile phone kept in the standby position could affect the testicular function and structure in the adult rabbit.

Falzone et al (2011) evaluated the effect of RF-EMF on sperm characteristics to assess the fertilizing potential of sperm. They exposed highly motile human spermatozoa to 900 MHz for an hour (SAR =2.0 W/kg) and examined effects at various time after exposure. The acrosome reaction was evaluated using flow cytometry. They did not find any effect on sperm propensity for the acrosome reaction. They obtained significant reduction in sperm head area (21.5±4% vs 35.5±11.4%) was obtained when compared among exposed and unexposed samples. Sperm zona binding was assessed directly after exposure. The mean number of zona-bound sperm of the test hemizona and controls was 22.8±12.4 and 31.8±12.8 ($p<0.05$) respectively. They concluded that though the radiation exposure did not adversely affect the acrosome reaction, it had a significant effect on sperm morphometry. They also observed a significant decrease in sperm binding to the hemizona. These data point toward sperm fertilization potential. These studies are in contradiction that fertility impairment was not caused by the induction of apoptosis in spermatozoa (Falzone et al 2010).

In a study undertaken by Ribeiro et al (2007), while experimenting with male Wistar rats, they exposed testis in the frequency and in the range of intensity (1835-1856 MHz, 0.04-1.4 mW/cm^2). The authors reported that the total body weight and absolute and relative testicular and epididymal weight did not change significantly, nor did the epididymal sperm count.

Human spermatozoa are known to be known to be vulnerable to oxidative stress because of abundant availability of substrates for free radical attack, and the lack of cytoplasmic space to accommodate antioxidant enzymes. The ROS generation does DNA damage, besides reducing fertility. The former has been linked with poor fertility, incidence of miscarriage and possible morbidity in the offspring, including childhood cancer.

There are other reports showing lack of effect on testicular function in experimental animals in the non-thermal range. They concluded that the responses are identical to those produced by hyperthermia caused by mere heating(Ribeiro et al 2007, Sommer et al 2009).

Comparison between non-modulated (DTX) and Modulated (Talk Signal) GSM Radiation

In an experimentation with insects, Panagopoulos (2011) divided these into two groups: a)the exposed (E) and b) the sham exposed (control) group (SE). Each of the two groups consisted of ten female and ten male newly emerged adult flies. The sham exposed groups had identical treatment as the exposed ones, except that the mobile phone during the “exposures” was turned off. The duration of exposure was 6 min per day in one dose extending over a period of 5 days.

In the first part of the exposure (1A) the insects were exposed in non-modulated GSM 900 MHz radiation (TDX-discontinuous transmission mode –signal) while in the second part (1B) they were exposed to modulated GSM 900 MHz radiation (or GSM talk signal). In both cases, the exposures were performed with the antenna of the mobile phone in contact with the walls of the glass vials containing the insects.

The difference between the modulated and the corresponding non-modulated GSM radiation is that the intensity of the modulated radiation is about ten times higher than the intensity of the corresponding non-modulated from the same handset (mobile phone) and additionally that the modulated radiation includes more and larger variations in its intensity within the same time interval, than the corresponding non-modulated one (Panagopoulos and Margaritis 2008). The power level of exposure for the modulated signal was 0.436±0.060 mW/cm^2 and the corresponding mean value for the non-modulated emission was (0.041±0.006) mW/cm^2. The measured ELF mean values of electric field intensity of the GSM signals excluding the ambient fields of 50 Hz were 6.05±1.02 V/m for modulated signal and 3.18±1.10 V/m for the non-modulated signal.

Experiments with the non-modulated GSM 900 MHz radiation (non-speaking mode of transmission) showed that this radiation decreased insect reproduction by an average of 18.24%. Correspondingly experiments with modulated GSM at 900 MHz (GSM "talk" signal) exposure shows that the radiation decreases reproduction by an average of 53.01 %. Above results indicate that the decrease in population is linked with intensity of the radiation. These authors concluded that between 900 MHz and 1800 MHz, the former is more bioactive owing to the difference in radiation intensity. Performing experiments at various distances (0 to 100cm) from mobile phone, Panagopoulos (2011) reported that the distance dependence is not linear. At the distances at 0 and 30 cm (intensity 378 μW/cm^2 and 10 μW/cm^2 respectively) show a maximum of decrease in reproductive capacity (window of maximum bioactivity). Correspondingly for GSM 1800 MHz at 0 and 20 cm (intensity 252μW/cm ^{2} and 11μW/cm^2 respectively) bioactivity is maximum (decrease in reproduction, window of maximum bioactivity) i.e. in the vicinity of free space wavelength of the corresponding radiation. For distances greater than 20 cm (up to 80 cm) the effect decreases rapidly and becomes very small for distances longer than 40 cm, but it is still evident for distances up to 80 cm (intensity down to 1.1μW/^{2}). These authors have further pointed out that it is the intensity which is primarily important rather than the frequency or the distance as such.

These distances (30 and 20 cm from GSM 900 MHz and GSM 1800 MHz correspond to the same RF intensity ($10\mu W/cm^2$) and also to the same electric field intensity of about 0.6-0.7 V/m. Maximum bioactivity is attributed to a distance of 0 cm or at approximately the two nodes of the wavelength, after which the effect declines. These authors reported no temperature increase inside any of the vials. They further concluded that the ELF components of digital mobile telephony signals that play a key role in their bioactivity, alone or in combination with the RF carrier signal . This also suggest that low frequency signals are more bioactive than higher frequency ones. Accordingly, electric field of the order of 10^{-3} V/m are able to disrupt cell function, perhaps by irregular gating of electrosensitive ion channels on the cell membranes. We conclude that both the GSM signal at 900 MHz and 1800 MHz fields appear to possess sufficient intensity for this for distances up to 50 cm from the antenna of a mobile phone (or about 50 m from a corresponding base station antenna). Therefore the restrictions being imposed on emission standards are with respect to continuous wave frequencies, but not with respect to a pulsed type, the latter being important in transmitting any intelligent information. Moreover real GSM signals are not constant in frequency and intensity. This distance of 20-30cm from the mobile phone corresponds to a distance of 20 to 30 m from a base station antenna. Panagopoulos et al (2010) showed that the bioactivity of GSM radiation in regard to short-term exposure is evident for radiation intensities down to $1\mu W/cm^2$. This value of radiation intensity is encountered at about 1m distance from a cell phone or about 100 m distance from a corresponding base station antenna. This radiation intensity is 450 times and 900 times lower than the ICNIRP limits for 900 and 1800 MHz respectively (ICNIRP,1998). It has been estimated by Panagopoulos (2011) that people may be exposed to this level of radiation for long distances so, a factor of ten could be added as a safety factor, thereby bringing down the above figure to 0.1 $\mu W/cm^2$, suggesting a limit for public exposure. These results support the findings that GSM radiation caused increased permeability of the blood –brain barrier in rat nerve cells and the strongest effect was produced by the SAR values which correspond to the weakest radiation intensity (Eberhardt et al.2008). The concept of window has earlier been described by Bawin et al (1978), Blackman et al (1980,1989). They have reported that the reproductive capacity decreases as the duration of exposure (1-21 minutes) increases(almost proportionally), for either of the two radiation types. Using statistical analysis they have confirmed that this variation is not because of the randomness of the subject, but because of the radiation exposure.

Several other authors have echoed a wide range of damaging effects on the male reproductive system and sperm parameters and cause significant changes in the sperm cell cycle (Derias et al 2006; Ji-Geng. 2007; Gutschi et al, 2011).

Non-genotoxic effects of Radiofrequency Radiation

Several studies reported no effect of RF fields on cell cycle kinetics (Vijayalaxmi et al 2001, Higashikubo et al 2001; Zeni et al, 2003; Miyakoshi et al, 2005; Lantow et al, 2006c). Alteration in cell proliferation was described only in a few reports (Pacini et al, 2002, Capri et al, 2004b).

Apoptosis is an important mechanism of protection against cancer. Several studies have reported RF field effects on human peripheral blood mononuclear cells (Capri et al, 2004a), lymphoblastoid cells (Marinelli et al, 2004), epidermis cancer cells (Caraglia et al 2005), and human Mono Mac 6 cells (Lantow et al, 2006c) and in Molts4 cells (Hook et al, 2004). No difference in apoptosis induction was detected between sham exposed and RF field exposed cells by Hook et al (2004). On the other hand, Marinelli et al (2004) have reported better survival rate of T lymphoblastoid leukaemia cells exposed to 900 MHz non-modulated RF fields and Carglia et al (2005) found apoptosis induction in human epidermoid cancer cells after exposure to 1.95 GHz fields. The European REFLEX study (Nikolova et al, 2005) reported no effects of RF fields on cell cycle, cell proliferation, cell differentiation, apoptosis induction, DNA synthesis and immune cell functionality. These authors described some findings after RF exposure on the transcript level of genes related to apoptosis and cell cycle control; however these responses were not associated with detectable changes of cell physiology. Analysis on whole genome cDNA arrays show alterations in gene expression after various RF exposure conditions using different cell types, but no consistent RF-signature such as stress response could be identified (Remondini et al, 2006).

Heat shock proteins act primarily as molecular chaperones to eliminate unfolded proteins, which can also appear from cellular stress. This stress response can be induced by many different external factors, including temperature, chemicals, oxidative stress, heavy metals, ionizing and non-ionizing radiation and ultrafine carbon black particles. Hsp70 has been shown to interfere with post mitochondrial events to prevent free radical mediated apoptosis (Gotoh et al 2001). An increased expression level of Hsp70 can thus offer protection against stress. Heat shock proteins are also involved in oncogenic processes (Jolly et al, 2000; Inoue et al, 1999; French et al, 2001).Some investigators have described increased heat shock

protein level after RF exposure (Leszczynski et al, 2002; Kwee et al, 2001). However, these results are controversial, because there are negative findings also (Cotgreave 2005).

Nikolova et al (2005) described modulation in gene regulation after RF field's exposure at a SAR of 1.5 W/kg in p53-deficient embryonic stem cells. Proteomic analyses of human endothelial cell lines showed RF fields induced changes in this expression and phosphorylation state of numerous proteins including the hsp27.

Mitochondrial generation of ROS : DNA fragmentation and Effects

Free radical formation and their interaction with biological system is a matter of major concern for it has health implications. There is evidence of free radical generation after RF-microwave exposures (Phillips et al 2009; De lullis et al 2009;Kesari and Behari 2012,Kesari et al 2012).

Mitochondrial respiratory chain is the major site for the generation of superoxide radicals (O_2 and H_2O_2). It is possible that EMF may affect the mitochondrial membranes to produce large amount of radicals ROS under experimental conditions. EMF may disturb ROS metabolism by increasing the production of ROS or by decreasing the activity of antioxidant enzymes. From the data presented here it is obvious that such a change in testes that is highly dependent on oxygen to drive spermatogenesis and yet highly susceptible to the toxic effects of reactive oxygen metabolites, activity of anti-oxidant enzymes, and increases in ROS production. Reactive oxygen species (ROS) such as superoxide anions (O^{-}), hydroxyl radicals (OH^{-}) and hydrogen peroxide ($H_2\ O_2$) may influence the structural integrity and function of sperm, such as motility, capacitation, and sperm-oocyte fusion (Griveau et al 1995). Spermatozoa are particularly vulnerable to oxidative stress because their plasma membrane is rich in polyunsaturated fatty acids (PUFAS) and membrane bound NADPH oxidase. Increased ROS production has been shown to correlate with reduced male fertility (Iwasaki and Gagnon 1992), to cause perioxidative damage to the sperm plasma membrane (Hughes et al 1996), and induce both DNA strand breakages and oxidative base damage in human sperm (Kodama et al 1997). A decrease in total antioxidant capacity of seminal plasma has been correlated with a reduction in sperm quality, such as concentration, motility and morphology (Smith et al 1996).

Since the most abundant molecule in biological cells is that of water (H_2O) microwave radiation can generate free radicals like OH^{-}, $O^{-}_{2,}$ H, and H^{-}. These molecules are extremely reactive, having a tendency to react with different biomolecules including DNA, because of an unpaired electron that they comprise, which try to give up this extra charge and go into the

paired mode. Also hydrogen peroxide (H_2O_2), a product of oxidative respiration in the mitochondria, which can be converted by electromagnetic radiation(EMR)into hydroxyl free radical via the Fenton reaction catalyzed by iron within the cells:

H_2O_2 + (EMR)-----→OH^-+OH^-

ROS generated by mobile phone exposure if not scavenged may lead to widespread lipid, protein, and DNA damage (Jajte et al 2002).

A summary of these results on Effects of Radiofrequency Microwave Radiation on Fertility and Reproduction is presented in Table 2.

The sequence of events leading toward infertility

A wide range of studies extending up to 50 GHz (Kesari and Behari 2009)) suggest that the DNA interaction with EMF is similar in nature across wide frequency ranges. DNA appears to possess the two structural characteristics of fractal antennas, electronic conduction and self- symmetry (Blank and Goodman 2011). These properties contribute to greater reactivity of DNA with EMF in the environment. The DNA damage could account for cancer promotion.

While damage to DNA has been confirmed in numerous scientific studies, it is argued that DNA repair is an on-going process and the damaged chromosomes can be reconstituted. However, this proposition is not without risk. There is no guarantee that these will replicate in the manner they were originally present. Pieces may be left out (deletions), joined in the backwards (inversions), swapped between different parts of the chromosomal (translocations)

Table 2: Overall effect of microwave radiation on reproduction and fertility

Organism used	**Mode of exposure**	**Parameters studied**	**Conclusion**	**Reference**
Fetus in the womb	laptop computers (LTCs)	induced currents in the body	power supply produces strong intracorporal electric current in the fetus and in the mother	Bellieni et al 2012
Sperm	Cell phone	Serum free testosterone (T), follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL)	Higher T and lower LH levels No change in FSH and PRL values	Gutschi et al, 2011
Male Wistar rats	2.45 GHz	Creatine and caspase	Increase in caspase and creatine kinase ; decreases in testosterone and melatonin	Kesari et al, 2011
human spermatozoa	900-MHz	Acrosomal reaction, Morphometric parameters	affect sperm morphometry decrease in sperm	Falzone et al, 2011
Male Sprague Dawley rat	1.95 GHz 5 h/d for 5 weeks	SOD, CAT, GPx, histone kinase,Apoptosis	No testicular toxicity.	Imai et al. 2011
male mice	mobile phone base stations	sperm head abnormalities	knobbed hook, pin-head and banana-shaped sperm head	Otitoloju et al, 2010
Drosophila melanogaster	GSM 900MHz and DCS 1800MHz	Reproductive capacity	cumulative effects on living organisms.	Panagopoulos and Margaritis, 2010

Table 2 continued ..

Drosophila melanogaster	900 MHz	ovarian size	Significant reduction in size of ovary	Panagopoulos and Margaritis 2010
Male Wistar rat	900 MHz 2 h d for 45 day	Sperm count, apoptosis	Reduced sperm count and increased apoptosis	Kesari et al 2010
Male Wistar rat	50GHz	SOD, CAT, GPx, histone kinase,Apoptosis	Decreased SOD,GPX and Histone kinase, increased CAT and apoptosis	Kesari and Behari 2010
Male rabbit	800 MHz 8 h /d 12 weeks	Sperm count, weights of testis, epididymis, seminal vesicles, and prostate	Drop in sperm count	Salama et al 2010
Male and female mice (C57BL)	1966 MHz (UMTS)	Semen analysis and sperm function tests	No change	Sommer et al 2009
Rat	mobile phones	volumes of the ovaries and follicles	reduction in number of follicles	Gul et al, 2009
human spermatozoa	1.8 GHz	motility and vitality	mitochondrial reactive oxygen species generation	De Iuliis et al , 2009
Wistar albino male rats	900 MHz 2 h/day (7 days/week) for 10 months	Apoptosis of testes	No effect on caspase-3 levels	Dasdag et al. 2008

Table 2 continued…

Male Wistar rat	50-GHz microwave radiation 2 h a day for 45 days at a power level of 0.86 μW/cm^2	DNA strand break, Apoptosis	Increased apoptosis and DNA strand break	Kesari & Behari, 2008
Male Sprague-Dawley rats	cellular phone emissions	sperm motility, sperm cell morphology, total sperm cell number, and mRNA levels	abnormal clumping of sperm cells	Yan et al 2007
Male Sprague-Dawley rats	cellular phone emissions for 18 weeks	sperm motility, sperm cell morphology, total sperm cell number, and mRNA levels	sperm cell death and , abnormal clumping of sperm cells	Ji-Geng et al , 2007
Mice	1800 MHz	Serum testosterone	No detectable changes	Forgács et al.2006
Human semen	cell phone	Semen analyses	negative effects on the sperm motility	Fejes, et al 2005
Male NMRI mice	1800 MHz(100μW 2 h	Steroidogenic Leydig cells	No change	Forgács et al 2005
Drosophila melanogaster	900-MHz	Reproductive capacity	decrease cellular processes during gonad development	Panagopoulos et al 2004
Pregnant rats	915MHz microwaves	uteroplacental circulation, and in placental endocrine and immune functions	No effects on blood estradiol and progesterone,	Nakamura et al, 2000
Sprague-Dawley rats	cellular phones 20 min per day (7 days a week) for 1 month	malondialdehyde ,p53 immune reactivity, sperm count, morphology,	No significant alteration	Dasdag et al, 2003

or even attached to the wrong chromosome. The effect may also be frequency dependent. In most cases, the new arrangement can work for a while if most of the genes are still present and any metabolic deficiencies can often be made good by the surrounding cells. However, things may be different if it comes to meiosis. During meiosis, the chromosomes line up in pairs (one from each original parent) along their entire length so that corresponding parts are adjacent and can be exchanged. Malformed pairs are torn apart in the later stages of meiosis so that eggs or sperms have an incomplete or unbalanced set of genes, may not function properly and so reduce fertility and other physiological functioning. There is a possibility that this may lead to permanent genetic damage, which though may not be visible in the first generation but may be thereafter. A summary of these results on Effects of Radiofrequency Microwave Radiation on Fertility and Reproduction is presented in Table 3.

Table 3: Overview of effects of Microwave radiation on reproductive patterns

Parameter studied	**900 MHz**	**2.45GHz**	**10GHz**	**50GHz**
PKC	↓	-	-	-
SOD	↓	↓	↓	↓
CAT	↑	↑	↑	↑
GPx	↓	↓	↓	↓
H1K	↓	-	↓	↓
DNA damage	↑	↑	↑	-
ROS	↑	↑	↑	-
CK	↑	↑	↑	-
Testosterone*	↓	↓	↓	-
Caspase*	↑	↑	↑	-

↑ Indicates significant increase ↓ Indicate significant decrease

(PKC: Protein kinase C; ODC: Ornithine decarboxylase; SOD: Superoxide dismutase; CAT: Catalase; GPx: Glutathione peroxidase; H1K: Histone kinase, CK: creatine kinase, ROS: reactive oxygen species)

* Some studies have reported that there is no significant changes in reproductive system.
* Forgács et al 2005,2006 (1800 MHz)
* Dasdag et al. 2008 (900 MHz)
* Imai et al. 2011 (1.95 GHz)
* Sommer et al 2009 (1966 MHz, UMTS)

VI. PRUDENT AVOIDANCE AND GUIDANCE FOR SAFETY LIMITS

While it appears to have been convincingly established that electromagnetic fields have adverse biological effects on fertility and reproduction, the emphasis is on 'use with caution' rather than no use at all. Children in the age 12 years and younger are more prone to the

damage because of their developing nervous system. Senior citizens and persons who are ill should also exercise caution and use wireless devices only in a most demanding situation. Mobile phones should thus be carried in close proximity of the body only in an OFF position (not ON and transmitting on standby). This is so because in an "standby" mode the phone emits signal intermittently - every few minutes they emit a periodic signal lasting a few seconds long - to maintain connection with the nearest base station antenna. These periodic signals are as powerful as the usual "talk signal" during a conversation. The user must make use of mobile phone speaker mode and keep the handset at least 40 cm away from their heads and other most sensitive organ like the head, heart and reproductive organs. Another method of protection (e.g. wired ear phones) are less effective, because of the existence of intensity window. The base station antennas should not be located within or near residential areas or near heavily populated areas. If antenna placement in the vicinity of residential zones is essential, they should be made to operate at substantially lowered power. Powerful wireless antennas should be placed on the hilltops and far from populated areas . The focus thus then shifts to prudent avoidance i.e. on to reduce the frequency and length of phone calls and keep away from these devices when not in use.

Bellieni et al (2012) have quoted that levels of exposure from "laptop" computers are higher than exposures that can be found in the proximity of high-voltage power lines and transformers or the domestic video screens .It has been observed that the magnetic field strength from power supplies is higher than that recommended by ICNIRP (1998) guidelines but that from LTC are within safe limits. It is thus suggested that use of LTC in an inclined position below the table level be avoided because it may cause increase in genital temperature ,besides causing back pain and fatigue. Moreover 'laptop' is a misnomer for its use in close proximity to the body is harmful.

Guidelines for Safety Limits

While considering the far field exposures, there are two sources: one is the microwave exposure from the base stations. While mobile phone exposure is localized, intermittent and is under voluntary control of the user, radiation from base towers is involuntary, whole-body and occurs 24 hours a day. While both the exposures may involve the same carrier frequency, the exposures are basically different in type and duration. On the whole it can be concluded that long term exposure near base stations can affect well-being of populations around them. Symptoms mostly associated with such exposures are headaches, tremor, restlessness and sleeping disorders.

The question of laying down the criteria for safe exposure is a problematic one, because the dose needs to be assessed not just as external field frequency (and spectrum), intensity, but also as cumulative exposure, as well as SAR, for whole body and specific anatomical sites. Accurate knowledge of RF exposure in a given scenario is needed for several parameters. The effect is not immediately visible but acts as silent killer. Any epidemiological studies for a long period (ten years or more) are difficult to carry under controllable situation, and few unexposed populations can serve as controls (non-exposed). Moreover the basic restrictions are expressed in quantities that are internal to the body and are not measured such as SAR. On the other hand, the reference levels are expressed (measured) in the free space situation, such as electric field. It is evident that SAR-concept alone is insufficient to define the safety guidelines for chronic exposure from mobile communications.

VI. CONCLUSIONS

Though causal evidence of one or more mechanism(s) are not yet fully refined, it is generally accepted that oxidative stress and free radical action may be responsible for the recorded genotoxic effects of EMFs which may lead to impairments in fertility and reproduction. Free radical action and/or hydrolytic enzymes like DNAase induced by exposure to EMFs may constitute the biochemical actions leading to adverse changes in hormones essential in males and female reproduction, DNA damage, which in turn causes damage to sperm motility, viability, and sperm morphology. Such exposures are now common in men who use and who wear wireless devices on their body, or use wireless-mode laptop computers. It may also account for damage to ovarian cells and female fertility, and miscarriage in women (ELF-EMF at 16 mG intermittent exposure).

VIII. REFERENCES

Agarwal A, Tamer M. Said TM. Role of sperm chromatin abnormalities and DNA damage in male infertility Human Reproduction Update 2003;9:331-345.

Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. Fertil Steril. 2008;89(1):124-8.

Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, et al. Effect of radiofrequency electromagnetic waves (RF-EMF) from cellular phones on human ejaculated semen: an in vitro study. Fertility Sterility 2009;92(4):1318-1325.

Aitken RJ, Bennetts LE, Sawyer D, Wiklendt AM, King BV. Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline. Int J Androl. 2005 Jun;28(3):171-9.

Aitken RJ, Roman SD. Antioxidant systems and oxidant stress in the testes. Review. Oxidative Med. Cell Longevity. 2008;1:15-24

Akdag MZ, Dasdag S, Aksen F, Isik B, Yilmaz F. Effect of ELF magnetic fields on lipid peroxidation, sperm count, p53, and trace elements. Med Sci Monit. 2006;12 (11):BR366-71.

Al-Akhras MA, Darmani H, Elbetieha A. Influence of 50 Hz magnetic field on sex hormones and other fertility parameters of adult male rats. Bioelectromagnetics 2006; 27(2):127-131.

Amara S, Abdelmelek H, Garrel C, Guiraud P, Douki Travant JL, et al. Effects of subchronic exposure to static magnetic field on testicular function in rats. Arch Med Res. 2006;37(8):947-52.

Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertility Sterlity 2012;97(1):39-45.

Bawin S, Adey W, Sabbot I. Ionic factors in release of 45 Ca2+ from chicken cerebral tissues by electromagnetic fields, In Proc. Natl. Acad. Sci. 1978;75(12):6314-6318.

Behari J, Kesari KK. Effects of microwave radiations on reproductive system of male rats. Embryo Talk 2006;1 (Suppl.1):81-5.

Bellieni CV, Pinto I, Bogi A, Zoppetti N, Andreuccetti D, Buonocore G. Exposure to electromagnetic fields from laptop use of “laptop” computers, Arch Environ Occup Health, 2012;67:1:31-36

Bernabo N, Tettamant E, Pistilli MG, Nardinocchi D, Beradinelli P, Mattioli M, Barboni B. Effects of 50 Hz extremely low frequency magnetic field on the morphology and function of boar spermatozoa capacitated in vitro. Theriogenology. 2007;67(4):801-815.

Bernabo N, Tettamant E, Pistilli MG, Nardinocchi D, Beradinelli P, Mattioli M, et al. Extremely low frequency electromagnetic field exposure affects fertilization outcome in swine animal model. Theriogenology. 2010;73(9):1293-1305.

Blackman CF, Benane SG, Elder JA, House DE, Lampe JA, Faulk JM.Induction of calcium-ion influx from tissue by radiofrequency radiation : Effect of sample number and modulation frequency on the power-density window. Bioelectromagnetics 1980;1:35-43.

Blackman CF, Kinney LS, House DE, Joines WT. Multiple power density windows and their origin. Bioelectromagnetics 1989;10(2):115-128.

Blank M, Goodman R. DNA is a fractal antenna in electromagnetic fields. Int J Radiation Biol 2011;87:409-415.

Cao XW, Zhao TD, Wang CH, Zhou Q, Li LQ, Yao HG, Zhang SQ, Tang, JT, Wei W. Alternating magnetic field damages the reproductive function of murine testes. Zhonghua Nan Ke Xue. 2009;15(6):530-533.

Capri M, Scarcella E, Fumelli C. Bianchi E, Salvioli S, Mesirca P. et al. In vitro exposure of human lymphocytes to 900 MHz CW and GSM modulated radiofrequency: studies of proliferation, apoptosis and mitochondrial membrane potential. Radiat Res. 2004a;162, 211-218.

Capri M, Scarcella E, Bianchi E, Fumelli C, Mesirca P, Agostini C, et al. 1800 MHz radiofrequency (mobile phones, different Global System for Mobile communication modulations) does not affect apoptosis and heat shock protein 70 level in peripheral blood mononuclear cells from young and old donors. Int J Radiat Biol. 2004b;80:389-397.

Caraglia M, Marra M, Mancinelli F, D'Ambrosio G, Massa R, Giordano A. et al. Electromagnetic fields at mobile phone frequency induce apoptosis and inactivation of the multi-chaperone complex in human epidermoid cancer cells. J Cell Physiol. 2005; 204:539-548.

Roychoudhury S, Massanyi P, Slamecka J, Chlebec I, Trandzik J, et al. In vitro gossypol induced spermatozoa motility alterations in rabbits. J Environ Sci Health B. 2009 Sep;44(7):730-41.

Chung MK, Lee SJ, Kim YB, Park SC, Shin DH, Kim SH, Kim JC. Evaluation of spermatogenesis and fertility in F1 male rats after in utero and neonatal exposure to extremely low frequency electromagnetic fields. Asian J Androl. 2005, 7(2):189-94.

Cotgreave IA. Biological stress responses to radio frequency electromagnetic radiation: are mobile phones really so (heat) shocking?, Arch Biochem Biophys. 2005;435:227–240.

Dasdag S, Akdag MZ, Aksen F, Yilmaz F, Bashan M, Dasdag M, Salih Celik M. Whole body exposure of rats to microwaves emitted from a cell phone does not affect the testes, Bioelectromagnetics 2003;24(3):182-188.

Dasdag S, Akdag MZ, Ulukaya E, Uzunlar AK, Yegin D. Mobile phone exposure does not induce apoptosis on spermatogenesis in rats. Arch Med Res. 2008 Jan;39(1):40-4.

Delgado JMR, Leal J, Monteagudo JL, Gracia MG. Embryological changes induced by weak, extremely low frequency electromagnetic fields. J Anat (Lond) 1982;134:533–552.

DeIullis GN, Newey RJ, King BV, Aitken RJ. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. PLos One 2009;4(7):e6446.

Deno DW, Zaffanella LE. Field effects of overhead transmission lines and stations, In Transmission Line Reference Book. 345 kV and above, 2nd edition , J J Ed. Project UHV, Technical Resource Operations. Large Transformer Division. General Electric Company, Pinsfield Mass. 1982;329/625.

Derias EM, Stefanis P, Drakeley, A, Gazvani R, Lewis_Jones DI. Growing concern over the safety of using mobile phones and male fertility. Arch. Androl. 2006;521:9-14.

Drozdov KA, Khlistun OA, Drozdov AL. The influence of ultrasound and constant magnetic field on gametes, zygotes, and embryos of the sea urchin. Biofizika. 2008; 53(3):513-518.

Eberhardt JL, Persson BR, Brun AE, Salford LG, Malmgren LO. Blood-brain barrier permeability and nerve cell damage in rat brain 14 and 28 days after exposure to microwaves from GSM mobile phones. Electromagn Biol Med. 2008;27(3):215-29.

Edwards MJ , Mulley R, Ring S, Warmer RA. Mitotic cell death and delay of mitotic activity in guinea pig embryos following brief material hyperthermia. J Embryol Exp Morphol 1974;32:593-602.

Erogul O, Oztas E, Yildirim I, Kir T, Aydur E, Komesli G, Irkilata HC, IrmakMK, Peker AF. Effects of electromagnetic radiation from a cellular phone on human sperm motility:an vitro study. Arch Med Res 2006;37(7):840-3.

Falzone N, Huyser C, Franken DR, Leszezynski D. Mobile phone radiation does not induce pro-apoptosis effects in human spermatozoa. Radiation Res 2010;174(2):169-76.

Falzone N, Huyser C, Becker P, Leszezynski DR, Franken DR. The effect of pulsed 900 MHz GSM mobile phone radiation on the acrosome reaction, head morphometry and zona binding of human spermatozoa. Int J Androl 2011;34(1):20-6.

Farrell JM Litovitz TL, Penafiel M, Montrose CJ, Doinov P, Barber M, et al. The effect of pulsed and sinusoidal magnetic fields on the morphology. Bioelectromagnetics. 1997;18:431-438.

Fraser FC, Skelton J (1978) Possible tetragenicity of maternal fever. Lancet 2:634.

Fejes I, Zavacki Z, Szollosi J, Koloszar Daru J, Kovacs L, Pal A. Is there a relationship between cell phone use and semen quality ? Arch Androl. 2005;51, 385-393.

Forgács Z, Kubinyi G, Sinay G, Bakos J, Hudák A, Surján A, Révész C, Thuróczy G. Effects of 1800 MHz GSM-like exposure on the gonadal function and hematological parameters of male mice. Magy Onkol. 2005;49(2):149-51. [Article in Hungarian]

Forgács Z, Somosy Z, Kubinyi G, Bakos J, Hudák A, Surján A, Thuróczy G. Effect of whole-body 1800 MHz GSM-like microwave exposure on testicular steroidogenesis and histology in mice. Reprod Toxicol. 2006; Jul;22(1):111-7.

French PW, PennyR, Laurence JA, McKenzie DR. Mobile phones, heat shock proteins and cancer. Differentiation 2001;67, 93-97.

García AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. Int J Epidemiol. 2008;37(2):329-40

Gharagozloo P, Aitken RJ. The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy. Hum Reprod 2011 Jul;26(7):1628-40. Epub 2011 May 5.

Gotoh T, Terada K, Mori M. hsp70-DnaJ chaperone pairs prevent nitric oxide-mediated apoptosis in RAW 264. 7 macrophages. Cell Death Differ. 2001; 8, 357-366.

Gul A, Celebi H, Ugras S. The effects of microwaves emitted by cellular phones on ovarian follicles in rats. Archives of Gynecology and Obstetrics 2009;280(5): 729-33.

Gutschi T, AI-Ali BM, Shamloul R, Pummer K, Trummer H. Impact of cell phone use on men's semen parameters. Andrologia. 2011;43, 5, 312–316.

Heredia-Rojas JA, Caballero-Hernandez DE, Rodriguez-de la Fuente AO, Ramos-Alfano G, Rodriguez-Flores LE. Lack of alterations on meiotic chromosomes and morphological characteristics of male germ cells in mice exposed to a 60 Hz and 2. 0 mT magnetic field. Bioelectromagnetics. 2004;25(1):63-8.

Hardell L, Sage C. Biological effects from electromagnetic field exposure and public exposure standards. Biomed Pharmacother. 2008;62(2):104-9.

Higashikubo R, Ragouzis M, Moros EG, Straube WL, Roti Roti JL. Radiofrequency electromagnetic fields do not alter the cell cycle progression of C3H 10T and U87MG cells. Radiat Res. 2001; 786–795.

Hong R, Liu Y, Yu YM, Hu K, Weng EQ. Effects of extremely low frequency electro magnetic fields on male reproduction in mice. Zhonghua Lao dong Wei Sheng, Zhi Ye Bing Za Zhi. 2003;21(5):342-345.

Hong R, Zhang V, Liu Y, Weng EQ. Effects of extremely low frequency electromagnetic fields on DNA of testicular cells and sperm chromatin structure in mice. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2005;23(6):414-417.

Hook GJ, Zhang P, Lagroye I, Li L, Higashikubo R, Moros EG, et al. Measurement of DNA damage and apoptosis in Molt-4 cells after in vitro exposure to radiofrequency radiation. Radiat Res. 2004; 161:193-200.

Hughes CM, Lewis SE, Mckelvey-Martin VJ, Thompson W. A comparison of baseline and induced DNA damage in human spermatozoa from fertile and infertile men, using a modified comet assay. Mol Hum Reprod. 1996; 13, 1240-1247.

Huss A, Spoerri A, Egger M, Röösli M and for the Swiss National Cohort Study. Residence near power lines and mortality from neurodegenerative diseases: longitudinal study of the Swiss Population. Am J Epidemiol. 2008;15, 169, 167-175.

ICNIRP. Guidelines for limiting exposure to time varying electric, magnetic, and electromagnetic fields (upto 300 GHZ) 1998. Health Phys. 1998;74:494-522.

Imai N, Kawabe M, Hikage T, Nojima T, Takahashi S, Shirai T. Effects on rat testis of 1. 95-GHz W-CDMA for IMT-2000 cellular phones. Syst Biol Reprod Med. 2011; Aug;57(4):204-9.

Inoue Y, Sato Y, Nishimura M, Seguchi M, Zaitsu Y, Yamada K. et al. Heat-induced drug resistance is associated with increased expression of Bcl-2 in HL60. Anticancer Res. 1999;19:3989-3992.

Iwasaki A, Gagon C. Formation of reactive oxygen species in spermatozoa of infertile patients. Fertil Steril. 1992; 57:409-416.

Jajte J, Grzegorczyk J, Zmyslony M, Rajkowska E. Effect of 7 mT static magnetic field and iron ions on rat lymphocytes: apoptosis, necrosis and free radical processes. Bioelectrochemistry. 2002;57:107-111.

Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Matloub HS. Effects of cellular phone emissions on sperm motility in rats. Fertility Sterility, 2007;88(4):957-964.

Jolly C, Morimoto RI. Role of the heat shock response and molecular chaperones in oncogenesis and cell death. J Natl Cancer Inst. 2000;92:1564 -1572.

Juutilainen J, Matilainen P, Saarikoski S, Läärä E, Suonio S. et al. Early pregnancy loss and exposure to 50 Hz magnetic fields. Bioelectromagnetics 1993;14:220-236.

Kesari KK, Behari J. Comparative study of 900MHz and 2. 45 GHz radiation effect on reproductive system of male rats. In: Recent Advances and Challenges in Reproductive Health Research. (RS Sharma, A Rajanna, M Rajalakshmi. Proceedings of the conference on "Recent Advances and Challenges in Reproductive Health Research (Feb 19-21, 2007 New Delhi) ICMR Publication, 2008.

Kesari KK, Behari J. Fifty gigahertz microwave exposure effect of radiation on rat brain. Appl Biochem Biotechnol 2009;158:126-139.

Kesari KK, Behari J. Microwave exposure affecting reproductive system in male rats. Appl Biochem Biotechnol. 2010;31(6):495-498.

Kesari KK, Behari J. Evidence for mobile phone radiation exposure effects on reproductive pattern of male rats: Role of ROS. Electromagnetics Biology Medicine. 2012;31(3):213-222.

Kesari KK, Kumar S, Nirala J, Siddiqui MH, Behari J. Biophysical evaluation of radiofrequency electromagnetic field effects on male reproductive pattern. Cell Biochem Biophys 2012;Aug 29;DOI 10. 1007/s12013-012-9414-6

Kesari KK, Kumar S, Behari J. Effects of radiofrequency electromagnetic wave exposure from cellular phones on the reproductive pattern in male Wistar rats. Appl Biochem Biotechnol 2011;164(4):546-59.

Kim YW, Kim HS, Lee JS, Kim YJ, Lee SK, Seo JN, Jung KC, Kim N, Gimm YM. Effects of 60 Hz 14 μT magnetic field on the apopotosis of testicular cell in mice. Bioelectromagnetics 2009;30(1):66-72.

Kilgalton SJ, Simmons LW. Image content influences men's semen quality. Biol Lett. 2005; 1, 385-393.

Kodama H, Yamaguchi R, Fukada J, Kasai H, Tanaka T. Increased oxidative deoxyribonucleic acid damage in the spermatozoa of infertile male patients. Fertil Steril. 1997;68, 519-524.

Kumar S, Kesari KK, Behari J. Evaluation of genotoxic effect in male wistar rats following microwave exposure. Ind J. Exp Biology 2010;48, 586-592.

Kumar S, Kesari KK, Behari J. The therapeutic effect of a pulsed electromagnetic field on the reproductive pattern of male wistar rats exposed to a 2. 45 GHz microwave field. Clinics 2011;66(7)1237-1245.

Kumar S, Kesari KK, Behari J. The influence of microwave exposure on male fertility. fertility and sterility. 2011a;95 (4); 1500-1502.

Kwee S, Raskmark P, Velizarov S. Changes in cellular proteins due to environmental nonionizing radiation. 1. Heat shock proteins. Electro- and Magnetobiol. 2001;20, 141-152.

Lacy KK, DeSesso JM, Lary JM. Early histological changes observed in the neural folds of day 9 rat embryos subsequent to radio frequency radiation or water bath induced hyperthermia. Teratology 1981;23:48A.

Lantow M, Viergutz T, Weiss DG, Simkó M. Comparative study of cell cycle kinetics and induction of apoptosis or necrosis after exposure to radiofrequency radiation in human Mono Mac 6 cells. Radiat Res. 2006c;166, 539-543.

Lee GM, Neutra RR, Hristova L, Yost M, Hatt RA. A nested case-control study of residential and personal magnetic field measures and miscarriages. Epidemiology 2001;13:21-31.

Leszczynski D, Joenväärä S, Reivinen J, Kuokka R. Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in human endothelial cells: molecular mechanism for cancer and blood-brain barrier-related effects. Differentiation 2002;2–3:120.

Li De-Kun, Checkoway H, Muller A. Electric blanket use during pregnancy in relation to the risk of congenital urinary tract anomalies among women with a history of subfertility. Epidemiology. 1995;6(5):485-489.

Lorio R, Scrimaglio R. Rantucci E, Delle Monache S, Di Gateano A, Finetti N, et al. A preliminary study of oscillating electromagnetic field effects on human spermatozoon motility. Bioelectromagnetics 2007;28(1): 72-75.

Lorio R, Delle Monache S, Bennato F, Di Bartolomeo C, Scrimaglio R, Cinque B, et al. Involvement of mitochondrial activity in mediating ELF-EMF stimulatory effect on human sperm motility. Bioelectromagnetics 2011;32 (1):15-27

Milan PB, Nejad DM, Ghanbari AA, Rad JS, Nasrabadi HT, Roudkenar MH, et al. Effects of Polygonum aviculare herbal extract on sperm parameters after EMF exposure in mouse. Pak J Biol Sci. 2011;1;14(13):720-4.

Marinelli F, La Sala D, Cicciotti G, Cattini L, Trimarchi C, Putti S, et al. Exposure to 900 MHz electromagnetic field induces an unbalance between pro-apoptotic and pro-survival signals in T-lymphoblastoid leukaemia CCRF-CEM cells. J Cell Physiol. 2004;198, 324-332.

Marx JL. Electric currents may guide development. Science 1981;211:1147-1149.

Miller P, Smith DW, Shepard TH. Material Hyperthermia as a possible cause of anencphaly. Lancet 1978;i:519-520.

Miyakoshi J, Takemasa K, Takashima Y, Ding GR, Hirose H, Koyama S. Effects of exposure to a 1950 MHz radio frequency field on expression of Hsp70 and Hsp27 in human glioma cells. Bioelectromagnetics 2005;26:251-257.

Nakamura H, Nagase H, Ogino K, Hatta K, Matsuzaki I. Uteroplacental circulatory disturbance mediated by prostaglandin f2alpha in rats exposed to microwaves. Reprod Toxicol. 2000;14(3):235-40.

Nikolova T, Czyz J, Rolletschek A, Blyszczuk P, Fuchs J, Jovtchev G, et al. Electromagnetic fields affect transcript levels of apoptosis-related genes in embryonic stem cell-derived neural progenitor cells. FASEB J. 2005;19:1686-1688.

O'Carroll MJ, Henshaw DL. Aggregating disparate epidemiological evidence: comparing two seminal EMF reviews. Risk Anal. 2008;28(1):225-34.

Otitoloju AA, Obe IA, Adewale OA, Otubanjo OA, Osunkalu VO. Preliminary study on the reduction of sperm head abnormalities in mice , Mus musculus, exposed to radiofrequency radiations from global system for mobile communication base stations. Bull Environ Contamin Toxicol 2010;84(1):51-4.

Pacini S, RuggieroM, Sardi I, Aterini S, Gulisano F, Gulisano M. Exposure to global system for mobile communication (GSM) cellular phone radiofrequency alters gene expression, proliferation, and morphology of human skin fibroblasts. Oncol Res. 2002; 1, 19–24.

Panagopoulos DJ, Karabarbounis A, Margaritis LH. Effect of GSM 900 MHz mobile phone radiation on the reproductive capacity of Drosophila melanogaster. Electromagnetic Biology and Medicine. 2004;23(1):29-43.

Panagopoulos DJ, Margaritis LH. Mobile Telephony radiation Efects on Living Organisms. In Harper A C and Buress R V (Eds) "Mobile Telephones Networks, Applications and Performance". Nova Science Publishers. 2008;107-149.

Panagopoulos DJ, Margaritis LH. Mobile telephony radiations. International Journal of Medical and Biological Frontiers. 2009;15(1-2), 33-76.

Panagopoulos DJ, Margaritis LH. The effects of exposure duration on the biological activity of mobile telephony radiation. International Journal of Radiation Biology. 2010;86(5):358-366.

Panagopoulos D J (2011)Analyzing the Health Impacts oF Modern Telecommunications Microwaves. Advances in Medicine and Biology. 17:1-54.

Phillips JL, Singh NP Lai H. Electromagnetic fields and DNA damage. Pathophysiology. 2009;16(23):79-88.

Polk C. Introduction. In: CRC Handbook of Biological Efects of Electromagnetic Fields (Polk C and Postow E) CRC Press, Inc Boca Raton, Florida. 1986;1-24.

Portier CJ, Wolfe MS, eds. EMF Science Review Symposium Breakout Group Reports for Theoretical Mechanisms and In Vitro Research Findings. Research Triangle Park: National Institute of Environmental Health Sciences, 1997.

Rajaei F, Borhani N, Sabbagh-Ziarani F, Mashayekhi F. Effects of extremely low-frequency electromagnetic field on fertility and heights of epithelial cells in pre-implantation stage endometrium and fallopian tube in mice. Zhong Xi Yi Jie He Xue Bao. 2010;8(1):56-60.

Remondini D, Nylund R, Reivinen J, Poulletier de Gannes F, Veyret B, et al. Gene expression changes in human cells after exposure to mobile phone microwaves. 2006;Proteomics, 6(17), 4745-4754.

Ribeiro EP, Rhoden EL, Horn MM, Rhoden C, Lima LP, Toniolo L. Effects of subchronic exposure to radiofrequency frequency from a conventional cellular telephone on testicular function in adult rats. J Urol 2007;177(1):395-9.

Roychoudhury S, Jedicka S, Parkanyl V, Rafay J, Ondruska L, Massanyl P, et al. Influence of a 50 Hz extremely low frequency electromagnetic field on spermatozoa motility and fertilization rats in rabbits. J Environ Sci Health A Tox Hazard subst Environ Eng. 2009;44(10):1041-1047.

Sage C, Johansson O, Sage SA. Personal digital assistant (PDA) cell phone units produce elevated extremely-low frequency electromagnetic field emissions. Bioelectromagnetics. 2007;28(5):386-392.

Salama N, Kishimoto T, Kanayama HO. Effects of exposure to a mobile phone on testicular function and structure in adult rabbit. International Journal of Andrology 2010;33(1):88-94.

Singh NP, Stephens RE. X-ray induced DNA double strand breaks in human sperm. Mutagenesis 1998;13:75-79.

Smith R, Vantman D, Ponce J, Escobar J, Lissi E. Total antioxidant capacity of human seminal plasma. Hum Reprod 1996;11:1655–60.

Sommer AM, Grote K, Reinhardt T, Streckert J, Hansen V, Lerchl A. Effects of radiofrequency electromagnetic fields (UMTS) on reproduction and development of mice: a multi-generation study. Radiation Research 2009;171(1):89-95.

Sun YL, Zhou WJ, Wu JQ, Gao ES. Does exposure to computers affect the routine parameters of semen quality? Asian J Androl 2005;; 7:263-266.

VanDemark NL, Free MJ. Temperature effects. IN Johnson AD, Gomes WR, VanDemark NL(eds): "The Testis, " Vol III. New York: Academic, 1970;233-312.

Vijayalaxmi, Bisht KS, Pickard WF, Meltz ML, Roti JL, Moros EG. Chromosome damage and micronucleus formation in human blood lymphocytes exposed in vitro to radiofrequency radiation at a cellular telephone frequency 1847-74 MHz CDMA. radiation Research. 2001;156:430-432.

Wang XW, Ding GR, Shi CH, Zeng, LH, Liu JY, Li J, et al. Mechanism involved in the blood-testis barrier increased permeability induced by EMP. Toxicology 2010;276:58-63.

Wdowiak A, Wdowiak L, Wiktor H. Evaluation of the effect of using mobile phones on male fertility. Annals Agriculture Environmental Medicine: AAEM 2007;14(1):169-72.

Wertheimer N, Leeper E. Possible effects of electric blankets and heated waterbeds on fetal development. Bioelectromagnetics 1986;7:13-22.

Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Metaloub HS. Effects of cellular phone emissions on sperm motility in rats. Fertility Sterility 2007;88(4): 957-64.

Zeni O, Chiavoni AS, Sannino A, Antolini A, Forigo D, Bersani F, et al. Lack of genotoxic effects (micronucleus induction) in human lymphocytes exposed in vitro to 900 electromagnetic fields. Radiat Res. 2003;160:152-158.

SECTION 19

Fetal and Neonatal Effects of EMF

Prof. Carlo V. Bellieni, MD
Neonatal Intensive Care Unit
University of Siena, Siena, Italy

Dr. Iole Pinto, PhD
Director, Physical Agents Laboratory
Tuscany Health and Safety Service, Siena, Italy

Prepared for the BioInitiative Working Group
September 2012

I. INTRODUCTION

The exposure of the developing fetus and of children to electromagnetic fields (EMF) including both radiofrequency radiation (RF) used in new wireless technologies, and to extremely low frequency or power frequency fields (ELF-EMF) has raised public health concerns because of the possible effects (cancer, neurological effects, developmental disability effects, etc) from the long-term exposure to low-intensity, environmental level fields in daily life. This chapter documents some studies on RF and ELF-EMF that report bioeffects and adverse health impacts to the fetus, and young child where exposure levels are still well within the current legal limits of many nations. Several studies report adverse health effects at levels below safety standards [Kheifets and Oksuzyan, 2008; Comba and Fazzo, 2009; World Health Organization. 2007]**;** the evidence to date suggests that special attention should be devoted to the protection of embryos, fetuses and newborns who can be exposed to many diverse frequencies and intensities of EMF throughout their lifetimes, where the health and wellness consequences on these subjects are still scarcely explored.

The studies of fetuses and newborns are an important subset of those made on older children. Infants' exposure to EMF has raised concern recently, and some countries have developed guidelines to limit it, by avoiding the presence of hospitals or schools within a certain range of kilometers around high EMF emission sources [http://www.emfs.info/Related+Issues/limits/]. Nevertheless, children and babies are chronically exposed to many sources of EMF, in particular at home, where they can spend much time playing with computers and other wireless-enabled devices, watching television or near electronic baby monitors that emit RF in their cribs (or sleeping areas). These exposures are relatively new in the last two decades, and may represent a potential new carcinogen and neurotoxin, that, with chronic and indiscriminate exposure, may have health consequences in the long term.

II. EMF AND RISK OF TUMORS

The evidentiary basis for evaluating an association between RF EMF exposure and brain cancer in children is much smaller than for adults [Wiedemann P, et al. 2009]. There is only one study available for mobile phone use. Elliott et al. [2010] found no association between risk of early childhood cancers (leukemia and non-Hodgkin's lymphoma, cancer of brain and central nervous system) and mothers' exposure to mobile phone base stations during pregnancy. Studies investigated brain cancer or leukemia with respect to EMF emitted from TV or radio transmitters

[Hocking et al. 1996; Dolk H, et al.1997; Cooper D, et al. 1997; Michelozzi P, et al. 2002; Park et al. 2004; McKenzie et al. 1998; Cooper et al. 2001; Maskarinec et al. 1994].

Few studies showed a significant increase of brain cancer in children with the use of cellular phones [Söderqvist et al. 2011; Merzenich et al. 2008], while some evidence exists for an association of RF EMF exposure to childhood leukemia. The argument for a causal influence of RF EMF exposure on leukemia in children is based on studies that found a statistically significant association between RF EMF exposure from radio or TV transmission towers and childhood leukemia. For instance, one case-control study [Ha, 2007.] found a significant increase for lymphocytic leukemia, but not for myelocytic leukemia in the highest exposure category.

Some authors suggested that genetic susceptibility to leukemia may amplify the adverse effects of magnetic field exposure, namely that the magnetic fields may have a causal role in the aetiology of leukemia among a genetically susceptible subgroup (i.e., children). For instance, Mejia-Arangure et al. [2007] observed a significant increase of childhood acute leukemia among Down syndrome subjects resident in dwellings with levels of magnetic flux density over 0.6 μT (OR= 3.7; 95% CI: 1.05-13.3). A recent paper [Kheifets and Oksuzyan, 2008] specifically addresses leukemia and it indicates as a priority the study of highly exposed children who live in apartments next to built-in transformers or electrical equipment rooms, emphasizing the investigation of joint effects of ELF environmental exposure and genetic co-factors.

III. EMF AND GENERAL HEALTH

Some studies address the question whether RF EMF exposure might cause general health disturbances in children [Milde-Busch et al. 2010; Heinrich et al. 2008; Divan et al. 2008; Söderqvist, 2008; Thomas, 2010; Vrijheid et al. 2010]. In a cross-sectional study Koivusilta et al. [2007] examined in a representative sample of 12–18-year-olds the association of mobile phone use with self- reported health status. Intensive use of communication technology, especially of mobile phones, was associated with health problems;. Van den Buick [2007] conducted a cohort study to assess the association between phone use by adolescents after lights out and levels of tiredness. Participants were adolescents with an average age of 14 in the youngest group and 17 in the oldest group. The authors found that those who used the mobile phone for calling and sending text messages after lights out were more likely to be very tired. Nevertheless, the results of these two studies were not proven to be due to EMF.

1V. EMF AND COGNITIVE FUNCTIONS

Original papers address the effect of RF EMF on cognitive function and CNS in children [Krause et al. 2006; Thomas et al. 2010; Abramson et al. 2009]. The age of the children investigated in these studies was in the range of 10–17 years. The argument supporting a causal influence of EMF exposure on cognitive function in children is based on the studies by several authors [Krause et al. 2006; Thomas et al. 2010; Abramson et al. 2009]. Lee et al [2001] administered three different tests that measure attention to 72 adolescents, who reported to either use a mobile phone or not. They found a statistically significant effect for one, the *Trail Making Test*. For the other two tests administered in the study, no statistically significant effects were found. The evidence for effects of RF EMF exposure on cognitive performance and CNS of children so far does not provide substantial hints for exposure-related changes. The very limited but provocative studies we do have suggest we cannot rule out that RF EMF exposure might influence cognitive and other CNS functions in children. If it is so, the consequences to public health can be enormous, if ignored.

V. FETUSES, NEWBORNS AND EMF

The early phases of human development have scarcely been studied with regard to their correlation with EMF. Nevertheless, the very young should receive more attention because of greater fragility and susceptibility of the developing embryo, fetus, and young child to environmental toxins of all kinds. Since fetuses and babies have a high number of stem cells and scarce immunity-mediated resources, any threat –in particular those due to physical and chemical agents – can have surprising and detrimental effects, since the environment influences even the DNA epigenetic expression [Davis and Lowell, 2008]. Czyz et al [2004] reported that GSM cell phone exposure affected gene expression levels in embryonic stem cells (p53-deficient); and significantly increased heat shock protein HSP 70 production. Belyaev et al [2010] reported that 915 MHz microwave exposure significantly affects human stem cells and may be important as a cancer risk. “The strongest microwave effects were always observed in stem cells. This result may suggest both significant misbalance in DSB repair, and severe stress response. Our findings that stem cells are the most sensitive to microwave exposure, and react to more frequencies than do differentiated cells may be important for cancer risk assessment and indicate that stem cells are the most relevant cellular model for validating safe mobile communication signals.”

In an animal study of mice, Aldad et al [2012] added support in a to the hypothesis that in-utero, whole-body exposure to RFR from cell phone radiation of the pregnant mother can result in hyperactivity, impaired memory and behavioral changes in the offspring.

Infante-Rivard and Deadman [2003] showed that maternal EMF exposure during pregnancy increased the risk of children 0-9 years of age developing leukemia (OR = 2.5, 95% CI = 1.2-3.0, for children of mothers in the highest 10% of exposure). Divan et al. [2008] reported that even prenatal exposure to cell-phone frequencies was associated with a significant increase in behavioral problems of emotion and hyperactivity around the age of school entry (OR = 1.80, 95% CI = 1.45-2.23). Although the results need replication, they point out an elevated susceptibility of the fetus and suggest a variety of adverse effects of cell-phone frequencies beyond just cancer. A recent study assessed that the exposure to EMF in pregnancy is linked to subsequent babies' asthma [Li et al. 2011].

Some researchers studied the possible effects of the exposure of fetuses to Magnetic Resonance Imaging (MRI) [Pediaditis et al. 2008]. Data seem to show that during abdominal MRI exposure limits of the mother "is not sufficient to protect the fetus if limits of the general populations are applied to it". In that case, fetal whole-body SAR exceeds limits by 7.4-fold. It is up to the physician and/or the ethics commission to decide upon justification for abdominal MRI of pregnant women if public safety limits are exceeded. The results indicate the need for specifically addressing fetal exposure to EMF and refining general recommendations by radiation protection bodies in line with the emerging science. Since the infant and young child are particularly vulnerable in general than adults, more care is needed to screen out unnecessary medical imaging of the pregnant woman and child and limit it to what is clearly medically necessary.

VI. LAPTOP COMPUTERS AND FETUSES

Bellieni et al [2012a] assessed EMF exposure levels of the 26-week fetus in the womb of a pregnant woman using a laptop computer in tight contact with pregnant women's belly. The word "laptop" means "a portable, usually battery-powered microcomputer small enough to rest on the user's lap," and this means that they are often used at close contact with the body in a very delicate area close to skin, bones, blood, genitals, and in the case of a pregnant woman, very close to her fetus. Since LTCs are often used in tight contact with the body even by pregnant women, fetal exposures to extremely low frequency (ELF-EMF) magnetic fields and induced electric currents within the fetus are generated by these units. These fields pass directly through the mother's tissues to the fetus. We measured the ELF-EMF emissions in five models of portable computers of

different brands. Experiments were performed using a NARDA ELF 400 electromagnetic field measuring system (1 Hz to 400 kHz range) after determining the ambient background level was no higher than 0.01 μT. The point of highest emission was measured at the surface of the laptop. The voxel model used to calculate intracorporal electric current density distributions was a whole-body human database of average pregnant woman, jointly developed by the National Institute of Information and Communications Technology and Ciba University, which represents a pregnant woman at the 26th week of gestation. In this model, mother and fetus tissues are defined according to NICT (National Institute of Information and Communications Technology) pregnant female voxel phantom. Dielectric properties of mother tissues are calculated using the parametric model developed by C. Gabriel and colleagues that reproduces the tissue conductivities in a wide range of frequencies. In the five brands of LTC we examined, ELF-EMF levels for their dominant frequency ranges from 1.8 to 6 μT, whereas those produced from the power supply ranges from 0.7 to 29.5 μT.

Induced electric currents were estimated for both the pregnant woman and the fetus. Statistical values of the averaged current density were evaluated for body tissues including the body of the fetus, and the grey and white matter of the brain of the mother; the mother's cerebellum, the mother's cerebrospinal fluid and mother's muscle tissue. In each case, the larger exposure was generated by the power supply rather than the laptop operation. Levels of induced current substantially exceeded ICNIRP public safety limits, assuming close proximity of the laptop to the belly of the pregnant woman (for the fetus, between 182% and 263.7% of the ICNIRP standard); and for the woman (between 346.7% and 483.5% of the ICNIRP standard).

Simple measures to distance the laptop during use (placing it on a table or desk and not on the body of the user) will result in significant reduction of ELF-EMF exposure and induced electric current in both mother and fetus.

VII. NEWBORN (INFANT) INCUBATORS

Fetuses can also be born prematurely, and very often are protected in neonatal incubators for several weeks. Only a few studies of incubators (or isolettes) have assessed ELF-EMF magnetic field exposures to the newborn baby inside an incubator where the source is a motor that generates these emissions. The motors of neonatal incubators produce electromagnetic fields in their vicinity. Although premature babies are often exposed to incubator ELF-EMF for months, little research has been done into the effects of EMFs on newborns, and most has regarded newborn

animals [Luchini and Parazzini, 1992; Watilliaux et al. 2011; Orendáčováet et al. 2011; Miyakoshi et al. 2012] so that the impact of this emission on the developing body's enhanced sensitivity to environmental insult is still largely unknown. In order to determine safe distances, ELF-EMF emissions must be measured and mapped, and these exposures need to be reduced to levels below that reported to cause adverse health effects in children (at or below 0.01 μT). To allow what is an essential medical intervention for the growing premature baby, or the sick infant who needs exceptional care following birth, at least two possible solutions to reduce ELF-EMF levels are:

- Designing incubators with the motor far from the baby (some incubators already have adopted this measure) and
- Using ELF-EMF absorbing panels to shield the baby's body from emissions (like Mu metal).

In Bellieni et al [2003], ELF-EMF levels are characterized in some common neonatal incubators. Levels of magnetic flux density at mattress level well over 10 milliGauss (mG) at mattress level: up to 88.4 mG in common incubators, and up to 357.0 mG in a transport incubator. These values are in line with those of two previous studies on ELF-EMFs in infant incubators[Lie and Kjaerheim, 2003; Babincova et al. 2000; Lie and Kjaerheim, 2003], and higher than the values recorded in two other reports [Aasen et al. 1996; Ramstad et al. 1998]. Another paper showed that nurses are also exposed to high EMF while working near incubators [Bellieni, 2002].

Bellieni et al [2008] reported that the exposure to high electromagnetic fields can interfere with the sympathetic nervous system in altering babies' heart rate variability. Heart rate variability (HRV) of 43 newborns in incubators was studied. HRV is an index of Autonomous Nervous System activity. The study group comprised 27 newborns whose HRV was studied throughout three 5-minute periods: 1) with incubator motor on, 2) with incubator off, and 3) with incubator on again, respectively. Mean HRV values obtained during each period were compared. The control group comprised 16 newborns but exposed to no source of ELF-EMF; they were exposed to changes in background noise similar to those provoked by the incubator motor (to reproduce the conditions of the first cohort). Mean total power and the high-frequency (HF) component of HRV increased significantly and the mean low-frequency (LF)/HF ratio decreased significantly when the incubator motor was turned off. Basal values were restored when incubators were turned on again. Changes in background noise did not provoke any significant change in HRV. We therefore concluded that ELF-EMFs produced by incubators influence newborns' HRV, showing an influence on their

autonomous nervous system. More research is needed to assess possible long-term consequences, since premature newborns may be exposed to these high ELF-EMFs for months.

Even melatonin production – as was signaled in adults [Wilson et al. 1989] – was inhibited in the newborn by exposure to ELF-EMF [Bellieni et al. 2012b]. The study concerned 28 babies (study group), who had spent at least 48-hr in common incubators with the presence of significant ELF-EMF. Measurements of mean 6-hydroxy-melatonin-sulfate (6OHMS) urine excretion were recorded at the end of their stay in the incubators, and compared with their mean 6OHMS excretion after having been put in cribs, where EMF are below the detectable limit (<0.01 μT). Mean 6OHMS/cr values were respectively 5.34±4.6 and 7.68±5.1ng/mg (p=0.026) when babies were exposed to ELF-EMF in incubators, and after having been put in the crib. We have compared these changes with a control group of babies, who were not exposed to EMF either before the first sampling nor before the second. We therefore measured urine 6OHMS twice, with an interval of 48-hr, in a control group of 27 babies who were not exposed to EMF during both samples. In the control group, mean 6OHMS/cr values in the first and in the second sample were respectively 5.91±5.41 vs 6.17±3.94 ng/mg (p=0.679). The transitory increase in melatonin production soon after removing newborns from incubators demonstrates a possible influence of EMF on melatonin production in newborns. We should point out that the two groups were similar in all but their mean corrected age. It was greater in the control group (the time as measured from conception).

VIII. CONCLUSIONS

Some studies [Lowenthal et al. 2007; Infante-Rivard and Deadman, 2003] report that the fetus and young children are at greater risk than are adults from exposure to environmental toxins. This is consistent with a large body of information showing that the fetus and young child are more vulnerable than older persons are to chemicals [Makri A, et al. 2004] and ionizing radiation [Preston, 2004]. These considerations have led the US Environmental Protection Agency (EPA) to propose a 10-fold risk adjustment for the first 2 years of life exposure to carcinogens, and a 3-fold adjustment for years 3 to 5 [http://www.epa.gov/sab/pdf/sab_04003_resp.pdf].

This susceptibility may be why, according to some authors (60)[Carpenter and Sage, 2008], “the evidence for the relation between magnetic field exposure and leukemia in children is stronger than that for adults”.

The World Health Organization Agency International Agency for Research on Cancer (or IARC) classifies both ELF-EMF and RF EMF as Possible Human Carcinogens or Group 2B [http://microwavenews.com/news/backissues/j-a01issue.pdf]. These proposed US EPA adjustments do not deal with fetal risk, and the possibility of extending this protection to the fetus should be examined, because of fetus' rapid organ development. Classification of these related electromagnetic field exposures (ELF-EMF and RF EMF) as having the potential for serious potential health consequences for adults certainly justifies additional protections for the fetus, the newborn and young children who have greater sensitive to such exposures. Further, there is good evidence to suggest that many toxic exposures to the fetus and very young child have especially detrimental consequences depending on when they occur during critical phases of growth and development (time windows of critical development), where such exposures may lay the seeds of health harm that develops even decades later. See Appendix 1 for international statements of concern and delineation of priority research needs published by the WHO and US National Academy of Sciences, National Research Council.

Important bioeffects and some adverse health effects of chronic exposure to low-intensity (non-thermal) non-ionizing radiation have been reported on babies, and important open questions still remain.

Existing FCC and ICNIRP public safety limits seem to be not sufficiently protective of public health, in particular for the young (embryo, fetus, neonate, very young child).

The World Health Organization International Agency for Research on Cancer has classified both ELF-EMF and RF EMF (wireless radiofrequency) as Possible Human Carcinogens (Group 2B).

New, biologically-based public exposure standards are critically needed.

Common sense measures to limit both ELF-EMF and RF EMF in these populations is needed, especially with respect to avoidable exposures like incubators that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RF EMF are easily instituted.

It is not in the public interest to wait: A precautionary approach may provide the frame for decision making where remediation actions have to be realized to prevent high exposures of children and pregnant woman.

APPENDIX 1

INTERNATIONAL STATEMENTS

World Health Organization Research Agenda for Radiofrequency Fields (2010) Children and EMF: Related Recommendations by World Health Groups

In 2010, the WHO produced a research agenda to address growing scientific questions and public concern about health effects of radiofrequency radiation, particularly with the explosive rise in exposures from new telecommunications technologies. It replaced a 2006 research agenda developed by the International EMF Project.

Priority: Epidemiology

> ***High -*** *Prospective cohort studies of children and adolescents with outcomes including behavioural and neurological disorders and cancer*
>
> *Rationale: As yet, little research has been conducted in children and adolescents and it is still an open question whether children are more susceptible to RF EMF since the brain continues to develop during childhood and adolescence. also, children are starting to use mobile phones at a younger age, given the existence of large-scale cohort studies of mothers and children with follow-up started during or before pregnancy, an RF sources component could be added at a reasonably low cost. Billing records for mobile phones are not valid for children, therefore the prospective collection of exposure data is needed. for neuropsychological studies, one challenge is to distinguish the "training" of motor and neuropsychological skills caused by the use of a mobile phone from the effects of the RF field. any future study should try to address this issue. in any case it should be of longitudinal design, thereby allowing the study of several outcomes and changes in technology and the use of mobile phones as well as other sources of RF EMF exposure, such as wireless laptops.*

Priority: Human studies

> ***High*** *- further RF EMF provocation studies on children of different ages*
>
> *Rationale: current research has focused primarily on adolescents; very little is known about possible effects in younger children. longitudinal testing at different ages, for example by studying children already participating in current cohort studies, is recommended. This would allow consideration of the influence of potentially confounding factors such as lifestyle.*

Priority: Animal studies

> ***High*** *- Effects of early-life and prenatal RF exposure on development and behaviour*
>
> *Rationale: There is still a paucity of information concerning the effects of prenatal and early life exposure to RF EMF on subsequent development and behaviour. Such studies are regarded as important because of the widespread use of mobile phones by children and the*

increasing exposure to other RF sources such as wireless local area networks (Wlans) and the reported effects of RF EMF on the adult EEG. Further study is required which should include partial (head only) exposure to mobile phones at relatively high specific absorption rate (SAR) levels.

National Research Council, National Academy of Sciences (2008)

The U.S. Food and Drug Administration (FDA) of the Department of Health and Human Services asked the National Academies to organize a workshop of national and international experts to identify research needs and gaps in knowledge of biological effects and adverse health outcomes of exposure to radiofrequency (RF) energy from wireless communications devices. To accomplish this task, the National Academies appointed a seven-member committee to plan the workshop (Committee on Identification of Research Needs Relating to Potential Biological or Adverse Health Effects of Wireless Communications Devices.). In their report, the Committee recommended these actions with respect to RF exposure for the developing fetus, and for young children:

- Characterization of exposure to juveniles, children, pregnant women, and fetuses from personal wireless devices and RF fields from base station antennas.

- Prospective epidemiologic cohort studies of children and pregnant women.

- Epidemiologic case-control studies and childhood cancers, including brain cancer.

IX. REFERENCES

Aasen SE, Johnsson A, Bratlid D, Cristensen T, 1996. Fifty Hertz magnetic field exposure of premature infants in a neonatal intensive care unit. Biol Neonat. **70**, 249–264.

Abramson MJ, Benke GP, Dimitriadis C, Inyang IO, Sim MR, Wolfe RS, et al. 2009. Mobile telephone use is associated with changes in cognitive function in young adolescents. Bioelectromagnetics, 30: 678–686.

Aldad TS, Gan G, Gao XB, Taylor HS. 2012. Fetal radiofrequency radiation exposure from 800-1900 MHz-rated cellular telephones affects neurodevelopment and behavior in mice. Sci Rep 2:312

Babincova M, P Sourivong, D Leszczynska, P Babinec. 2000. Influence of alternating magnetic fields on two-dimensional tumor growth. Electro-Magnetobiol. **19**, 351–355.

Bellieni CV, Acampa M, Maffei M, Maffei S, Perrone S, Pinto I, Stacchini N, Buonocore G. 2008. Electromagnetic fields produced by incubators influence heart rate variability in newborns. Arch Dis Child Fetal Neonatal Ed. 93(4):F298-301.

Bellieni CV, Pinto I, Bogi A, Zoppetti N. 2012a. Andreuccetti D, Buonocore G. Exposure to electromagnetic fields from laptop use of "laptop" computers. Arch Environ Occup Health. 67(1):31-6

Bellieni CV, Rigato M., M. Fortunato, D. M. Cordelli, and F. Bagnoli, 2003. Increasing the distance bed-engine: A way to decrease EMF in incubators. IJP **29**, 74–80.

Bellieni CV, Tei M, Iacoponi F, Tataranno ML, Negro S, Proietti F, Longini M, Perrone S, Buonocore G. 2012b. Is newborn melatonin production influenced by magnetic fields produced by incubators? Early Hum Dev. 2012 Aug;88(8):707-10.

Bellieni CV. 2002. Esposizione del personale infermieristico ai campi elettromagnetici in TIN. Assist Inferm Ric. **21**:28–31.

Belyaev I, Markova E, Malmgren L. [2010] Microwaves from Mobile Phones Inhibit 53BP1 Focus Formation in Human Stem Cells Stronger than in Differentiated Cells: Possible Mechanistic Link to Cancer Risk. Environ Health Perspect. 118(3): 394–399.

Carpenter DO, Sage C. 2008. Setting prudent public health policy for electromagnetic field exposures. Rev Environ Health 23(2):91-117.

Comba P, Fazzo L. 2009. Health effects of magnetic fields generated from power lines: new clues for an old puzzle. *Ann Ist Super Sanità*; 45, (3): 233-237

Cooper D, Hemming K, Saunders P. 1997. Cancer incidence near radio and television transmitters in Great Britain. I. Sutton Coldfield transmitter. Am J Epidemiol, 145: 1–9.

Cooper D, Hemmings K, Saunders P. 2001. Re: .Cancer incidence near radio and television transmitters in Great Britain. I. Sutton Coldfield transmitter; II. All high power transmitters..

Am J Epidemiol, 153:202–205.

Czyz J, Guan K, Zeng Q, Nikolova T, Meister A, Schönborn F, Schuderer J, Kuster N, Wobus AM. 2004. High frequency electromagnetic fields (GSM signals) affect gene expression levels in tumor suppressor p53-deficient embryonic stem cells. Bioelectromagnetics. 25(4):296-307

Davis GE, Lowell WE. 2008. Peaks of solar cycles affect the gender ratio. Med Hypotheses. 71(6):829-38.

Divan HA, Kheifets L, Obel C, Olsen J. 2008. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. Epidemiology, 19: 523–529.

Divan HA, Kheifets L, Obel C, Olsen J. 2008. Prenatal and postnatal exposure to cell phone use and behavioral problems in children. Epidemiology. 19(4):523-9.

Dolk H, Elliott P, Shaddick G, Walls P, Thakrar B. 1997. Cancer incidence near radio and television transmitters in Great Britain. II. All high power transmitters. Am J Epidemiol, 145: 10–17, 1997.

Elliott P, Toledano MB, Bennett J, Beale L, de Hoogh K, Best N, et al. 2010. Mobile phone base stations and early childhood cancers: case-control study. BMJ, 340: c3077.

Environmental Protection Agency. Response to the SAB Review Panel's Recommendations on the Draft Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens. Available at the following URL: http://www.epa.gov/sab/pdf/sab_04003_resp.pdf

Ha M, Im H, Lee M, Kim HJ, Kim BC, Gimm YM, et al. 2007. Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancer. Am J Epidemiol, 166: 270–279.

Heinrich S, Kühnlein A, Thomas S, et al. 2008. Epidemiologische Untersuchung zu möglichen akuten gesundheitlichen Effekten durch Mobilfunk bei Kindern und Jugendlichen (Abschlussbericht). 2008 [cited 2009 July]; Available from: http://www.emf-forschungsprogramm.de/forschung/epidemiologie/epidemiologie_verg/epi_045.html.

Hocking B, Gordon IR, Grain HL, Hatfield GE. 1996. Cancer incidence and mortality and proximity to TV towers. Med J Aust, 165: 601–605.

Infante-Rivard C, Deadman JE. 2003. Maternal occupational exposure to extremely low frequency magnetic fields during pregnancy and childhood leukemia. Epidemiology. 14(4):437-41.

Infante-Rivard C, Deadman JE. 2003. Maternal occupational exposure to extremely low frequency magnetic fields during pregnancy and childhood leukemia. Epidemiology. 14(4):437-41.

Kheifets L, Oksuzyan S. 2008. Exposure assessment and other challenges in nonionizing radiation studies on childhood leukemia. Radiat Prot Dosimetry 2008;132:139-47.

Kheifets L, Oksuzyan S. 2008. Exposure assessment and other challenges in nonionizing radiation studies on childhood leukemia. Radiat Prot Dosimetry 132:139-47.

Koivusilta LK, Lintonen TP, Rimpela AH. 2007. Orientations in adolescent use of information and communication technology: a digital divide by sociodemographic background, educational career, and health. Scand J Public Health, 35: 95–103.

Krause CM, Björnberg CH, Pesonen M, Hulten A, Liesivuori T, Koivisto M, et al. 2006. Mobile phone effects on children's event-related oscillatory EEG during an auditory memory task. Int J Radiat Biol, 82: 443–450.

Lee, TMC , Ho, SMY , Tsang, LYH , Yang, SYC , Li, LSW , Chan, CCH. 2001. Effect on human attention of exposure to the electromagnetic field emitted by mobile phones. Neuroreport, 12(4), 729-731

Li DK, Chen H, Odouli R. 2011. Maternal exposure to magnetic fields during pregnancy in relation to the risk of asthma in offspring. Arch Pediatr Adolesc Med. 165(10):945-50.

Lie JA, Kjaerheim K. 2003 Cancer risk among female nurses: A literature review. Eur J Cancer Prev. **12**, 517–526.

Lie JA, Kjaerheim K. 2003. Cancer risk among female nurses: A literature review. Eur J Cancer Prev. **12:**517–526.

Lowenthal RM, Tuck DM, Bray IC. 2007. Residential exposure to electric power transmission lines and risk of lymphoproliferative and myeloproliferative disorders: a case-control study. Intern Med J. 37(9):614-9

Luchini L, Parazzini F. 1992. [Exposure to low-frequency electromagnetic fields and pregnancy outcome: a review of the literature with particular attention to exposure to video terminals]. Ann Ostet Ginecol Med Perinat. 113(2):102-13.

Makri A, Goveia M, Balbus J, Parkin R. 2004. Children's susceptibility to chemicals: a review by developmental stage. J Toxicol Environ Health B Crit Rev. 2004 Nov-Dec;7(6):417-35

Maskarinec G, Cooper J, Swygert L. 1994. Investigation of increased incidence in childhood leukemia near radio towers in Hawaii: preliminary observations. J Environ Pathol Toxicol Oncol, 13: 33–37.

McKenzie DR, Yin Y, Morrell S. 1998. Childhood incidence of acute lymphoblastic leukemia and exposure to broadcast radiation in Sydney – a second look. Aust N Z J Public Health, 22(3 Suppl): 360–367.

Mejia-Arangure JM, Fajardo-Gutierrez A, Perez-Saldivar ML, Gorodezky C, Martinez-Avalos A, Romero-Guzman L, et al. 2007. Magnetic fields and acute leukemia in children with Down Syndrome. Epidemiology 18:158-61.

Merzenich H, Schmiedel S, Bennack S, Brüggemeyer H, Philipp J, Blettner M, et al. 2008. Childhood leukemia in relation to radio frequency electromagnetic fields in the vicinity of TV

and radio broadcast transmitters. Am J Epidemiol, 168: 1169–1178.

Michelozzi P, Capon A, Kirchmayer U, Forastiere F, Biggeri A, Barca A, et al. 2002. Adult and childhood leukemia near a high-power radio station in Rome, Italy. Am J Epidemiol, 155: 1096–1103.

Milde-Busch A, von Kries R, Thomas S, et al. 2010. The association between use of electronic media and prevalence of headache in adolescents: results froma population-based cross-sectional study. BMC Neurology, 10: 12, 2010.

Miyakoshi Y, Kajihara C, Shimizu H, Yanagisawa H. 2012. Tempol suppresses micronuclei formation in astrocytes of newborn rats exposed to 50-Hz, 10-mT electromagnetic fields under bleomycin administration. Mutat Res. 747(1):138-41.

Orendáčová J, Orendáč M, Mojžiš M, Labun J, Martončíková M, Saganová K, Lievajová K, Blaško J, Abdiová H, Gálik J, Račeková E. 2011. Effects of short-duration electromagnetic radiation on early postnatal neurogenesis in rats: Fos and NADPH-d histochemical studies. Acta Histochem. 113(7):723-8.

Park SK, HaM, ImHJ. 2004. Ecological study on residences in the vicinity of AM radio broadcasting towers and cancer death: preliminary observations in Korea. Int Arch Occup Environ Health, 77: 387–394.

Pediaditis M, Leitgeb N, Cech R. 2008. RF-EMF exposure of fetus and mother during magnetic resonance imaging. Phys Med Biol. 2008 Dec 21;53(24):7187-95.

Preston RJ. 2004. Children as a sensitive subpopulation for the risk assessment process. Toxicol Appl Pharmacol. 199(2):132-41.

Ramstad S and Bratlid, D, Christensen T, Johnsonn A. 1998. Infants in an intensive care unit. The electromagnetic field environment. HK J. Pediatr. **3**, 15–20.

Söderqvist F, Carlberg M, Hansson Mild K, Hardell L. 2011. Childhood brain tumour risk and its association with wireless phones: a commentary. Environ Health. 2011 Dec 19;10:106.

Söderqvist F, Carlberg M, Hardell L. 2008. Use of wireless telephones and self-reported health symptoms: a population-based study among Swedish adolescents aged 15–19 years. Environ Health, 7(1): 18.

Thomas S, Benke G, Dimitriadis C, Inyang I, Sim MR, Wolfe R, et al. 2010. Use of mobile phones and changes in cognitive function in adolescents. Occup Environ Med, 67: 861–866.

Thomas S, Heinrich S, von Kries R, Radon K. 2010. Exposure to radio-frequency electromagnetic fields and behavioural problems in Bavarian children and adolescents. Eur J Epidemiol, 25: 135–141.

Van den Buick J. 2007. Adolescent use of mobile phones for calling and for sending text messages after lights out: results from a prospective cohort study with a one-year follow-up. Sleep, 30: 1220–1223.

Vrijheid M, Martinez D, Forns J, Guxens M, Julvez J, Ferrer M, et al. 2010. Prenatal exposure to cell phone use and neurodevelopment at 14 months. Epidemiology, 21: 259–262.

Watilliaux A, Edeline JM, Lévêque P, Jay TM, Mallat M. 2011. Effect of exposure to 1,800 MHz electromagnetic fields on heat shock proteins and glial cells in the brain of developing rats. Neurotox Res. 20(2):109-19.

Wiedemann P, et al. 2009. Schütz H, Börner F, Berg-Beckhoff G, Croft R, Lerchl A, Martens L, Neubauer G, Regel S, Repacholi M: Children's health and RF EMF exposure. Forschungszentrum Jülich GmbH. Available at the following URL: http://juwel.fz-juelich.de:8080/dspace/bitstream/2128/3683/1/Gesundheit_16.pdf

Wilson BW, Stevens RG, Anderson LE. 1989. Neuroendocrine mediated effects of electromagnetic-field exposure: possible role of the pineal gland. Life Sci. 45(15):1319-32.

World Health Organization. 2007. *Extremely low frequency fields*. Geneva: WHO; (Environ Health Criteria n. 238).