Chapter 5

Genotoxicity by Electromagnetic Fields

José Antonio Heredia-Rojas,
Ricardo A. Gómez-Flores, Eulogio De la Cruz-Torres,
Omar Heredia-Rodríguez,
Eduardo Campos-Góngora,
Pedro César Cantú-Martínez,
Laura E. Rodríguez-Flores and
Abraham O. Rodríguez-de la Fuente

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74128

Abstract

Modern life implies a constant exposure of living organisms to many sources of radiation, especially electromagnetic fields (EMFs) generated by our technological devices. The question of whether or not EMFs in the non-ionizing extremely low frequency (ELF) range can induce genotoxic effects is currently a subject of interest. People of industrialized societies are commonly exposed to EMFs and waves in a very broad range of frequencies, including power lines, telecommunications, and domestic and industrial equipment. In this review, we present controversial evidence from our research group and others of genotoxicity induced by ELF-EMFs, since scientific community consider EMF devices produce marginal amounts of energy, which does not justify any DNA alterations, together with conflicting laboratory results and few epidemiological studies. However, in 2002 the International Agency for Research on Cancer (IARC) categorized ELF-EMFs as being potential carcinogenic and genotoxic agents to humans. The aim of the present chapter is to discuss the role of ELM-EMFs on human genotoxicity.

Keywords: genotoxicity, human DNA, non-ionizing radiation, electromagnetic fields, low-frequency radiation, extremely low frequency radiation

1. Introduction

Human exposure to electromagnetic fields (EMFs) and waves is a common feature of modern life. We have learned to understand the physical characteristics of these energy forms, and have applied them in many ways to embellish our ways of life and our standards of living. Furthermore, individuals have become dependent on them for health, safety, information, comfort, and conveyance. In fact, it has been determined that living in a major metropolitan region will increase at least three-fold exposure to environmental EMFs, than that of people living in suburban of rural areas, although the level of exposure depends on the proximity and time of exposure to a radiation source.

EMFs and waves are reported to produce direct and indirect effects on genes and chromosomes of living beings, which depend on many physical, chemical, and biological factors. They may be visible or not soon after exposure. However, there may be subtle changes only detectable upon careful laboratory study, or be apparent after a long period of time.

Our understanding of the interaction of EMFs with living systems is progressing in a wide range of areas. Nowadays, the increasing amount of research related to the evaluation of EMFs genotoxic effects, lead to consider the potential risk associated with EMFs exposure. In the last 4 decades, research on the genotoxic and cytotoxic effects and health implications of EMFs, not only has expanded, but also has become a subject of a public concern and private debate worldwide.

It is known that the interaction of EMFs and waves with biological systems is frequency-dependent. High frequencies possess more energy and different interaction mechanisms than the low ones. The focus of this chapter is on the recent developments and our experience on living systems interaction of very-low and extremely-low EMF frequencies.

2. Electromagnetic fields and waves

Although gamma and X-rays, ultraviolet rays, visible light, infrared radiation, microwaves, radiofrequency, and slowly varying electric and magnetic fields are typical of the electromagnetic spectrum, they differ in their interaction with physical materials and living organisms. This difference mainly resides in their specific wavelength, since they all travel at the speed of light. The energy of these waves propagates in bundles of photons, and the energy in a photon is inversely proportional to the wavelength. Therefore, the shorter the wavelength, the higher the energy per photon. Clearly, the photon energies vary over a wide range of values [1].

Gamma rays and X-rays possess high amounts of energy and are capable of ionization, that is, they produce ions by ejection of orbital electrons from the atoms of the material thorough which they travel [2]. Their biological effects, therefore, result largely from the produced ionization. On the other hand, in the non-ionizing region of the spectrum, ultraviolet radiation is important for a number of biological processes and has also been shown to have deleterious effects on many biological activities [3]; one common effect of ultraviolet radiation is sunburn. Ultraviolet is known to kill several microorganisms and is reported to have carcinogenic effects as well. It transmits its energy to atoms or molecules almost entirely by excitation, that is, it promotes electrons to higher orbits. Consequently, some of the effects produced by ultraviolet radiation may resemble the changes resulting from ionizing radiation. In fact, ultraviolet radiation is considered the limit value between ionizing and non-ionizing radiation.

In regard to non-ionizing radiation, photosynthesis, plant growth, and vision depend on visible light. These wavelengths are no capable of ionization nor excitation, but they produce photochemical or photobiological reactions. Infrared radiation from the sun is the major source of the Earth's heat, and it is also emitted by all living beings. There is little evidence showing that photons in the infrared region are capable of initiating photochemical reactions in biological materials [4]. Although thermochemical reactions may follow photochemical reactions, changes in vibrational modes are responsible for absorption in the infrared region. The absorbed energy increases the kinetic energy of the system, which in turn, is dissipated in the form of heat. Thus, the primary response of biological systems to infrared exposure is thermal. It is customary to use frequency instead of wavelength to denote electromagnetic energy at the microwave range and below. The microwave region extends from 300 mHz to 300 GHz, radiofrequency from 30 kHz to 300 MHz, VLF (very low frequency) from 3 to 30 kHz, and ELF (extremely low frequency) ranges from 3 Hz to 3 kHz, which includes the power system frequency of 50–60 Hz. Microwave and radiofrequency fields primarily increase the kinetic energy of the exposed systems, upon absorption by the biological materials [5]. In this case, the increased energy is due to changes of the vibrational or rotational energy state that dissipates into heat.

At VLF and ELF frequencies, EMFs have wavelengths that are much larger than typical dimensions of life bodies. The electric and magnetic fields become quasi-static and can be considered separately. Because the living organisms contain almost no magnetic material, lower frequency magnetic fields can penetrate without attenuation. Furthermore, electric fields are induced within the life bodies by these time-varying magnetic fields and cause the so-called "Eddy currents" to flow inside the body. These currents represent the primary biological effect attributed to such ELF-EMFs.

An important characteristic of the effect of ionizing and non-ionizing (photochemical reactions produced by absorbed light) energies on humans is that they are cumulative. However, at present there is no scientific evidence indicating any cumulative effect due to exposure to electromagnetic energy in the microwave, radiofrequency, and the lower frequency region. Available information suggests that the observed effects diminish as the intensity is reduced to a low level and repeated exposures do not seem to deviate from this conclusion [5]. This is probably because at low levels, the organism has an opportunity for recovery to an injury (if any) from exposure; however, it is uncertain if prolonged exposure to low level ELF fields has seriously harmful biological effects, such as genotoxic or carcinogenic is still open.

Penetration of ELF-EMFs to tissues increases with frequencies. For instance, at 50–60 Hz, the internal electric field (IEF) of a person standing under a powerline is about 10^{-6} times weaker than that with the external field strength. The marginal IEF under such conditions become one of the reasons why research on ELF health effects has focused on magnetic fields. In contrast, low-frequency magnetic fields are not attenuated by biological tissues, thus the internal and external magnetic field intensities are identical. EMF energy absorption by humans is the highest between 30 and 300 mHz, which is the resonance range for the whole body. Above this, EMFs penetrate the human tissues as electromagnetic waves, rather than separate electric and magnetic fields. Furthermore, at the microwave range, electromagnetic waves penetration depth decreases with increasing frequency [6].

In order to understand the genotoxic and cytotoxic effects attributed to ELF-EMFs, it is necessary to consider the electromagnetic induction. Magnetic fields induce electrical currents in conductors. Cells and tissues are affected by these currents (as mentioned before, the so-called "Eddy Currents"), with the increase of frequencies the magnitude of the induced current increases. Strong magnetic fields lead to changes in orientation, rotation and movement, and deformation and fusion or destruction of cells. Quantum processes are not possible, because the quantum energy of the fields is not big enough to break molecular bonds, as an ionizing radiation does [7].

3. Carcinogenesis

Electromagnetic fields at very- and extremely-low frequency regions, were classified as "possibly carcinogenic" by the International Agency for Research on Cancer [8], based on pooled analyses of epidemiological research that reported an association between exposure to low-level magnetic fields and several types of cancer.

As genetic damage is very often a signal for cancer, some publications have reported associations between EMF exposure and DNA damage [9–11], but other studies showed conflicting results [12–14]. In this regard, several epidemiological studies support a weak to moderate association between exposure to magnetic fields in residential or occupational environments and the incidence of cancer [15–17], particularly acute leukemia and brain cancer. An association between EMFs exposure and cancer has been suggested, but it has not been evidenced, however, a number of well-designed residential and occupational studies are underway. A solid case for causality will depend on various factors including consistent associations of magnetic fields and cancer, improved exposure characterization, dose-response data, and full evaluation of potential confounding factors. The very complex phenomenon of carcinogenesis suggests that ELF-EMFs can alter cell growth in many ways involving hormone secretion. Melatonin, the principal pineal hormone, exerts a suppressive action on other endocrine glands. Reduced circulating concentrations of melatonin can result in increased prolactin release by the pituitary and increased estrogen and testosterone release by the gonads. ELF-EMFs have been reported to suppress melatonin production by the pineal gland [18–20]. On the basis of these findings, it may be postulated that magnetic fields may increase the risk of certain hormone-dependent cancers, i.e. breast and prostatic carcinomas.

At present, the available information suggests that ELF-EMFs may cause cancer. Much research (epidemiology, animal bioassays, mechanistic studies, and basic biology), however, remains to be done in order to assess the full carcinogenesis potential of ELF-EMFs and to evaluate, in quantitative terms, the level of risk of ELF-EMFs intensities in the order of magnitude to which humans are currently being exposed. ELF-EMFs then represent one of the priority issues on environmental and occupational carcinogenesis. Our knowledge of the carcinogenicity of ELF-EMFs leads to a wider concern about possible similar effects of non-ionizing electromagnetic radiation other than ELF-EMFs. In future characterizations of possible cancer risk, considerable reliance will probably be given to laboratory investigations which will, on demand, include genotoxicity research.

4. The genotoxic potential of magnetic fields

Biological effects of magnetic fields have been widely discussed during recent years. The question has been raised as to whether exposure to such fields causes genetic damage. Many researchers agree that life bodies could be genetically affected by exposure to magnetic fields [21–25]. Nevertheless, the issue of ELM-EMFs genotoxic potential is controversial, mainly related to the fact that many scientists believe ELF-EMF devices emit low energy and are therefore too weak to have any effect on cells. Because of the low energy levels in molecular interactions, it is physically highly improbable that ELF-EMFs cause direct genetic damage. However, it has been theorized that these fields may enhance such damage from other sources, e.g. endogenous radicals [26]. Furthermore, the inconclusive nature of laboratory experiments turns this concern more conflicting. Regarding the issue that weak fields may have too low energy to cause genotoxic effect or DNA damage, it has been proposed that because low frequency electromagnetic radiation does not transmit enough energy to alter chemical bonds, ELF-EMFs do not directly damage DNA [13, 27, 28]. However, several hypotheses of the indirect effect of EMFs on DNA structure, have been suggested. For this, secondary currents and, hence, a movement of electrons in DNA might be induced [29, 30]. This may, in turn, produce guanine radicals, which, upon reaction with water, induce oxidative DNA damage [31, 32]. Recently, Focke et al. [33] reported that exposure of human primary fibroblasts to a 50 Hz EMF at 1.0 mT caused a slight, but significant increase of DNA fragmentation, as tested by the Comet assay. They also showed that EMF-induced responses in this assay were dependent on cell proliferation, suggesting that processes of DNA replication, rather than the DNA itself may be affected.

Three important reviews published in the 90s [6, 34, 35] and recently by Maes and Verschaeve [26], concluded that ELF-EMFs do not directly cause genotoxic effects. Only a small minority of the reported studies indicate potential of these fields to cause genetic changes in biological systems. A few studies have addressed the possibility that ELF-EMFs could enhance the action of known genotoxic chemicals or ionizing radiation. There is some evidence that ELF-EMFs might enhance the genotoxic potential of gamma radiation [36], X-rays [37]; or mutagenic chemicals [38].

A critical review by Vijayalaxmi and Obe [39] concluded that 22% of previous studies of ELF-EMF-induced genotoxicity indicated a genotoxic effect, whereas 46% did not and 32% of the studies were inconclusive. Recently, Dominici et al. [40] reported a significant high micronuclei frequency in human blood cells of welders exposed to ELF-EMF, in a dose-dependent manner. Yaguchi et al. [41, 42] also showed that exposure to 5, 50, and 400 mT ELF-EMF can induce sister chromatid exchanges and chromosomal aberrations in murine m5S cells. Similarly, Lai and Singh [43] observed genotoxic effects of these fields, finding that exposure of rats for 2 h to a 60 Hz magnetic field (0.1, 0.25, and 0.5 mT) increased DNA strand breaks in brain cells in a dose-dependent fashion, indicating a clastogenic effect.

In relation to ELF-EMF long exposures, Rageh et al. [44] observed a significant increase in rat bone marrow micronuclei continuously exposed for 30 days to 50 Hz and 0.5 mT magnetic fields, suggesting an association between ELF-EMF exposure time and DNA damage. In contrast, Abramsson-Zetterberg and Grawé [45], reported that an 18-day exposure to 50 Hz and 14 μT magnetic fields did not significantly alter micronucleated red cells frequency in fetal and adult mice.

Despite the large number of published works in recent years, there is no conclusive evidence supporting causality of exposure to ELF-EMFs and genotoxicity.

5. Our experience regarding genotoxicity induced by ELF-EMFs

In view of these conflicting results, several years ago we developed some studies aimed to evaluate the genotoxic and cytotoxic potential of ELF-EMFs. In a report by Heredia-Rojas et al. [46], lack of genotoxic effect of 60 Hz magnetic fields on sister-chromatid exchange (SCE) frequency of cultured human peripheral blood lymphocytes, but altered cell proliferation, as measured by proliferation (PI) and mitotic (MI) indexes, were observed; exposed lymphocytes showed higher PI and MI than controls. It was also shown no synergistic effect of magnetic fields and mitomycin-C (a well-known genotoxic agent) on SCE frequency. However, PI and MI in cultures treated with mitomycin-C and exposed to magnetic fields were higher than those in cultures treated with mitomycin-C alone, indicating that proliferating activity increase may increase the overall risk of mitomycin-C induced genomic damage [46].

The issue of potential genotoxic and cytotoxic effects of magnetic fields in the ELF region has developed almost completely from cytological studies in somatic cells. However, meiotic cells offer a good model to establish a relationship between magnetic field exposure and cytotoxicity. Based on this, we evaluated the effect of *in vivo* exposure of mice to a 60 Hz sinusoidal magnetic field at 2.0 mT on male germ cells. No statistically significant differences on meiotic chromosome aberrations in spermatocytes and sperm morphology were observed between magnetic field-exposed and control animals. Furthermore, when animals were co-exposed to magnetic fields and mitomycin-C, an antagonistic effect in terms of meiotic chromosome aberrations and sperm morphology abnormalities were observed. Treated animals showed, in spite of mitomycin-C genotoxicity, lower percentages of meiotic chromosome aberrations and sperm morphology abnormalities, when compared with animals treated with mitomycin-C alone [47].

5.1. Effects of ELF-EMFs on immune function

It has been proposed that the effects of ELF-EMFs depend on the biological-functional state of the cells, in particular on the degree of cellular activation for cells of the immune system, and this is correlated with genetic damage. For that reason, we decided to perform bioassays trying to demonstrate the ELF-EMFs effects on immune parameters. We have previously reported absence of proliferation of murine thymic lymphocytes, production of nitric oxide and phagocytosis of *Candida albicans* by peritoneal murine macrophages effects after 60 Hz and 1.0 mT treatment [48]. In contrast, 72 h exposure to 60 Hz and 2.0 mT oscillating magnetic fields significantly increased number of apoptotic-like cells and cellular immune response in *Trichoplusia ni* (Lepidoptera:Noctuidae) larvae [49]. Furthermore, conflicting results on the effect of ELF-EMFs on the immune system have been reported [50, 51].

5.2. Effects of ELF-EMFs on gene expression

It has been reported that 50–60 Hz magnetic fields with flux densities ranging from microTesla to milliTesla, induce changes in gene expression, and this in turn, can increase the overall risk for genotoxicity, which is considered in the search of gene-environment interactions. Based on this, we have evaluated the effect of 60 Hz sinusoidal magnetic fields at 8.0 and 80.0 μT on expression of the luciferase gene, contained in an own gene construct labeled as electromagnetic field-plasmid (pEMF), which was transfected into HeLa and BMK16 cell lines, later exposed to magnetic fields; this vector included the hsp70 promotor containing the 3 nCTCTn sequences, previously described for the induction of hsp70 expression by magnetic fields, as well as the reporter of the luciferase gene [52]. For this bioassay, a positive control of thermal shock treated cells was included. Interestingly, we observed an increased luciferase expression after exposure to magnetic fields and thermal shock, compared with controls. Furthermore, a synergistic effect between two factors on luciferase gene expression, was observed [52]. In another study, Heredia-Rojas et al. [53], demonstrated that a magnetic field with characteristics aforementioned, increased luciferase gene expression and activity in INER-37 cells. However, this treatment had no effect on RMA E7 cells [53]. Recently, Rodríguez-de la Fuente et al. [54], showed significant luciferase expression increase in mice exposed to ELF-EMFs (80 μT and 60 Hz frequency) for 2 h a day for 7 days, with prior pEMF vector electro-transferred to BALB/c mice quadriceps muscles, as compared with controls. Our work of magnetic field effects on gene expression was summarized in a recent book chapter [55].

Taking together, the resulting research data, along with other reports by others, suggest that ELF-EMFs are involved in DNA damage.

5.3. ELF-EMFs in pre-clinical studies

There is an increasing interest in the use of magnetic fields in medicine. The notion that magnetic fields can be used for therapeutic purposes has existed long before they were understood or were controllable. Particularly, pulsed electromagnetic fields (PEMFs) technology was based on 2 decades of studies related to the electromechanical properties of bone and other connective tissues. Effectiveness of such fields to treat a number of health conditions has been recently demonstrated.

We have evaluated the genotoxic effect induced in PEMF-exposed rats, using a patented medical device (US patent 6,235,251 B1). The cytological endpoints included acridine orange fluorescent-staining micronucleus test and male germ cells analysis and the observed results showed that the applied magnetic fields generated by the therapeutic device did not have any detectable genotoxic effect in exposed rats, compared with the unexposed controls [56].

In addition, we have reported a clastogenic effect of 60 Hz magnetic fields on mice bone marrow, as assessed by *in vivo* micronucleus (MN) test [57]. As mentioned before, it is accepted that ELF-EMFs do not cause breaks in DNA because they are unable to transfer energy to cells in sufficient amounts to damage DNA directly and thus, in the past they were considered to be non-genotoxic. Nevertheless, we observed a higher MN frequency in mice exposed to 60 Hz magnetic fields at 1.5 and 2.0 mT, compared with controls. Recommendations by Vijayalaxmi and Obe [39] due to the conflicting nature of laboratory experiments and variability, we decided to develop three independent experiments at three different times and in three different laboratories located in our Department of Exact Sciences and Human Development in Biological Sciences School at Autonomous University of Nuevo Leon, Mexico, the Department of Pathology in Medicine School at this University, and the Institute of Biomedicine at the Mexican Institute of Social Security, Mexico. A high MN frequency in exposed animals was observed in all bioassays. For acute treatments, an exposure time of 72 h was chosen because it is generally accepted that the period of differentiation from stem cells to mature erythrocytes in mice is about 72 h [58]. In addition, it was reported the same antagonistic effect between ELF-EMF exposure and mitomycin-C, as previously observed in cultured human lymphocytes and mice germ cells mentioned above [46, 47].

6. Concluding remarks

It is clear that the current knowledge of bioeffects of weak magnetic fields is limited and inconclusive to establish a causality with genotoxic effects. However, evidence is beginning to accumulate both from epidemiological studies and laboratory work that might be enlightening to define genotoxic risks involved with exposure to ELF-EMFs. Further studies are needed to clarify this and consequently the interaction mechanisms involved.

The absence of independent replication has been a consistent feature of experimental studies searching for biological effects of weak ELF-EMFs. It remains to be determined whether the present reports on DNA damage will be substantiated, demonstrating a potential relevance to a chain of events leading to genotoxicity, which is considered the gold standard to define if an environmental factor is a carcinogen, but the currently available data for extremely-low frequency time-varying magnetic fields remain conflicting. As an environmental stimulus, the effect of ELF-EMFs on cellular DNA may be subtle. Therefore, a more sensitive method and systematic research strategy are warranted to evaluate genotoxicity. Meanwhile, we believe it would be a good practice to adopt the discreet avoidance strategy. Environmental EMFs are generated, in part, by the transmission and distribution of 60 Hz electric power using overhead lines and by those of electricity in residential buildings, and in the workplace. Other sources, in particular inductive devices such as electric motors, also generate localized, relatively intense magnetic fields. Regarding the workplace or home environment, this could include the choosing of low emission appliances when new equipment is considered, and switching off the apparatus when not in use.

Acknowledgements

The authors are grateful to the Director of the Instituto de Investigaciones Biomédicas del Noreste del Instituto Mexicano del Seguro Social, México, Dr. Javier Vargas-Villarreal, for critically revising the manuscript.

Conflict of interest

The authors claim they have no conflicts of interest to declare.

Author details

José Antonio Heredia-Rojas[1], Ricardo A. Gómez-Flores[2], Eulogio De la Cruz-Torres[3], Omar Heredia-Rodríguez[1], Eduardo Campos-Góngora[4], Pedro César Cantú-Martínez[1], Laura E. Rodríguez-Flores[5] and Abraham O. Rodríguez-de la Fuente[1]*

*Address all correspondence to: abraham.rodriguezd@uanl.edu.mx

1 Department of Exact Sciences and Human Development, Biological Sciences School, Autonomous University of Nuevo Leon, México

2 Department of Microbiology and Immunology, Biological Sciences School, Autonomous University of Nuevo Leon, México

3 National Institute of Nuclear Research, México

4 Public Health and Nutrition School, Autonomous University of Nuevo Leon, México

5 Medicine School, Autonomous University of Nuevo Leon, México

References

[1] Parker SP, editor. Encyclopedia of Physics. 2nd ed. N.Y. USA: McGraw-Hill; 1993. 1141 p

[2] Casarett AP. Radiation Biology. Englewood Cliffs, New Jersey: Prentice-Hall; 1968. pp. 27-30

[3] Diffey BL. Solar ultraviolet radiation effects on biological systems. Physics in Medicine and Biology. 1999;**36**:299-328

[4] Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. Journal of Photochemistry and Photobiology B: Biology. 1999;**49**:1-17. DOI: 10.1016/S1011-1344(98)00219-X

[5] Lin JC, editor. Advances in Electromagnetic Fields in Living Systems. Vol. I. NY: Plenum Press; 1994. pp. 1-25. DOI: 10.1007/978-0-387-92736-7

[6] Juutilainen J, Lang S. Genotoxic, carcinogenic and teratogenic effects of electromagnetic fields. Introduction and overview. Mutation Research/Reviews in Mutation Research. 1997;**387**:165-171. DOI: 10.1016/S1383-5742(97)00036-7

[7] Kaiser F. External signals and internal oscillation dynamics: Biophysical aspects and modelling approaches for interaction of weak electromagnetic fields at the cellular level. Bioelectrochemistry. 1996;**41**:3-18. DOI: 10.1016/0302-4598(96)05085-4

[8] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, Part I: Static and extremely low-frequency (ELF) electric and magnetic fields. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2002;**80**:1-395

[9] Karaca E, Durmaz B, Aktug H, Yildiz T, Guducu C, Irgi M, Koksal MG, Ozkinay F, Gunduz C, Cogulu O. The genotoxic effect of radiofrequency waves on mouse brain. Journal of Neuro-Oncology. 2012;**106**:53-58. DOI: 10.1007/s11060-011-0644-z

[10] Liu C, Duan W, Xu S, Chen C, He M, Zhang L, Yu Z, Zhou Z. Exposure to 1800 MHz radiofrequency electromagnetic radiation induces oxidative DNA base damage in a mouse spermatocyte-derived cell line. Toxicology Letters. 2013;**218**:2-9. DOI: 10.1016/j.toxlet.2013.01.003

[11] Panagopoulos DJ, Karabarbounis A, Lioliousis C. ELF alternating magnetic field decreases reproduction by DNA damage induction. Cell Biochemistry and Biophysics. 2013;**67**:703-716. DOI: 10.1007/s12013-013-9560-5

[12] Hintzsche H, Jastrow C, Kleine-Ostmann T, Kärst U, Schrader T, Stopper H. Terahertz electromagnetic fields (0.106 THz) do not induce manifest genomic damage in vitro. PLoS One. 2012;**7**(9):e46397. DOI: 10.1371/journal.pone.0046397

[13] Bouwens M, de Kleijn S, Ferwerda G, Cuppen JJ, Savelkoul HF, Kemenade BM. Low-frequency electromagnetic fields do not alter responses of inflammatory genes and proteins in human monocytes and immune cell lines. Bioelectromagnetics. 2012;**33**:226-237. DOI: 10.1002/bem.20695

[14] Xu S, Chen G, Chen C, Sun C, Zhang D, Murbach M, Kuster N, Zeng Q, Xu Z. Cell type-dependent induction of DNA damage by 1800 MHz radiofrequency electromagnetic fields does not result in significant cellular dysfunctions. PLoS One. 2013;**8**(1):e54906. DOI: 10.1371/journal.pone.0054906

[15] Wertheimer N, Leeper E. Electrical wiring configurations and childhood cancer. American Journal of Epidemiology. 1979;**109**:273-284

[16] Kheifets L, Ahlbom A, Crespi CM, Feychting M, Johansen C, Monroe J, Murphy MF, Oksuzyan S, Preston-Martin S, Roman E, Saito T, Savitz D, Schüz J, Simpson J, Swanson J, Tynes T, Verkasalo P, Mezei G. A pooled analysis of extremely low-frequency magnetic fields and childhood brain tumors. American Journal of Epidemiology. 2010;**172**:752-761. DOI: 10.1093/aje/kwq181

[17] Schüz J. Exposure to extremely low-frequency magnetic fields and the risk of childhood cancer: Update of the epidemiological evidence. Progress in Biophysics and Molecular Biology. 2011;**107**:339-342. DOI: 10.1016/j.pbiomolbio.2011.09.008

[18] Welker HA, Semm P, Willig RP, Commentz JC, Wiltschko W, Vollrath L. Effects of an artificial magnetic field on serotonin N-acetyltransferase activity and melatonin content of the rat pineal gland. Experimental Brain Research. 1983;**50**:426-432

[19] Liboff AR. Why are living things sensitive to weak magnetic fields? Electromagnetic Biology and Medicine. 2014;**33**:241-245. DOI: 10.3109/15368378.2013.809579

[20] Selmaoui B. Effects of extremely low frequency (ELF) and radio-frequency (RF) on melatonin and cortisol, two markers of the circadian rhythms. Toxicology Letters. 2017;**280**: S31. DOI: 10.1016/j.toxlet.2017.07.076

[21] Ivancsits S, Diem E, Pilger A, Rüdiger HW, Jahn O. Induction of DNA strand breaks by intermittent exposure to extremely-low-frequency electromagnetic fields in human diploid fibroblasts. Mutation Research. 2002;**519**:1-13

[22] Feychting M, Ahlbom A, Kheifets L. EMF and health. Annual Review of Public Health. 2005;**26**:165-189. DOI: 10.1146/annurev.publhealth.26.021304.144445

[23] Ghodbane S, Lahbib A, Sakly M, Abdelmelek H. Bioeffects of static magnetic fields: Oxidative stress, genotoxic effects, and cancer studies. BioMed Research International. 2013;**2013**:602987. DOI: 10.1155/2013/602987

[24] Mihai CT, Brinza F, Vochita G, Rotinberg P. Extremely low-frequency electromagnetic fields cause DNA strand breaks in normal cells. Journal of Environmental Health Science and Engineering. 2014;**12**:15. DOI: 10.1186/2052-336X-12-15

[25] Maes A, Anthonissen R, Wambacq S, Simons K, Verschaeve L. The cytome assay as a tool to investigate the possible association between exposure to extreme low frequency magnetic fields and an increased risk for Alzheimer's disease. Journal of Alzheimer's Disease. 2016;**50**:741-749. DOI: 10.3233/JAD-150669

[26] Maes A, Verschaeve L. Genetic damage in humans exposed to extremely low-frequency electromagnetic fields. Archives of Toxicology. 2016;**90**:2337-2348. DOI: 10.1007/s00204-016-1769-9

[27] Luceri C, De Filippo C, Giovanelli L, Blangiardo M, Cavalieri D, Aglietti F, Pampaloni M, Andreuccetti D, Pieri L, Bambi F, Biggeri A, Dolara P. Extremely low-frequency electromagnetic fields do not affect DNA damage and gene expression profiles of yeast and human lymphocytes. Radiation Research. 2005;**164**:277-285

[28] Lupke M, Frahm J, Lantow M, Maercker C, Remondini D, Bersani F, Simkó M. Gene expression analysis of ELF-MF exposed human monocytes indicating the involvement of the alternative activation pathway. Biochimica et Biophysica Acta. 2006;**1763**:402-412. DOI: 10.1016/j.bbamcr.2006.03.003

[29] Valberg PA, Kavet R, Rafferty CN. Can low level 50/60 Hz electric and magnetic fields cause biological effects? Radiation Research. 1997;**148**:2-21

[30] Lin H, Blank M, Rossol-Haseroth K, Goodman R. Regulating genes with electromagnetic response elements. Journal of Cellular Biochemistry. 2001;**81**:143-148

[31] Giese B, Amaudrut J, Köhler AK, Spormann M, Wessely S. Direct observation of hole transfer through DNA by hopping between adenine bases and by tunnelling. Nature. 2001;**412**(6844):318-320. DOI: 10.1038/35085542

[32] Giese B. Electron transfer through DNA and peptides. Bioorganic & Medicinal Chemistry. 2006;**14**:6139-6143. DOI: 10.1016/j.bmc.2006.05.067

[33] Focke F, Schuermann D, Kuster N, Schär P. DNA fragmentation in human fibroblasts under extremely low frequency electromagnetic field exposure. Mutation Research. 2010;**683**:74-83. DOI: 10.1016/j.mrfmmm.2009.10.012

[34] McCann J, Dietrich F, Rafferty C, Martin AO. A critical review of the genotoxic potential of electric and magnetic fields. Mutation Research. 1993;**297**:61-95

[35] McCann J, Dietrich F, Rafferty C. The genotoxic potential of electric and magnetic fields: An update. Mutation Research. 1998;**411**:45-86

[36] Hinterlang D. Synergistic effects of ionizing radiation and 60 Hz magnetic fields. Bioelectromagnetics. 1993;**14**:545-551

[37] Miyakoshi J, Yamagishi N, Ohtsu S, Mohri K, Takebe H. Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations by exposure to high-density 50-Hz magnetic fields. Mutation Research. 1996;**349**:109-114

[38] Tabrah FL, Mower HF, Batkin S, Greenwood PB. Enhanced mutagenic effect of a 60 Hz time-varying magnetic field on numbers of azide-induced TA100 revertant colonies. Bioelectromagnetics. 1994;**15**:85-93

[39] Vijayalaxmi RL, Obe G. Controversial cytogenetic observations in mammalian somatic cells exposed to extremely low frequency electromagnetic radiation: A review and future research recommendations. Bioelectromagnetics. 2005;**26**:412-430. DOI: 10.1002/bem.20111

[40] Dominici L, Villarini M, Fatigoni C, Monarca S, Moretti M. Genotoxic hazard evaluation in welders occupationally exposed to extremely low-frequency magnetic fields (ELF-MF). International Journal of Hygiene and Environmental Health. 2011;**215**:68-75. DOI: 10.1016/j.ijheh.2011.07.010

[41] Yaguchi H, Yoshida M, Ejima Y, Miyakoshi J. Effect of high-density extremely low frequency magnetic field in sister chromatid exchanges in mouse m5S cells. Mutation Research. 1999;**440**:189-194

[42] Yaguchi H, Yoshida M, Ding GR, Shingu K, Miyakoshi J. Increased chromatid-type chromosomal aberrations in mouse m5S cells exposed to power-line frequency magnetic fields. International Journal of Radiation Biology. 2000;**76**:1677-1684

[43] Lai H, Singh NP. Acute exposure to 60 Hz magnetic field increases DNA strand breaks in rat brain cells. Bioelectromagnetics. 1997;**18**:156-165

[44] Rageh MM, El-Gebaly RH, El-Bialy NS. Assessment of genotoxic and cytotoxic hazards in brain and bone marrow cells of newborn rats exposed to extremely low-frequency magnetic field. Journal of Biomedicine and Biotechnology. 2012;**2012**:1-7. DOI: 10.1155/2012/716023

[45] Abramsson-Zetterberg L, Grawé J. Extended exposure of adult and fetal mice to 50 Hz magnetic field does not increase the incidence of micronuclei in erythrocytes. Bioelectromagnetics. 2001;**22**:351-357

[46] Heredia-Rojas JA, Rodríguez-de la Fuente AO, Velasco-Campos MR, Leal-Garza CH, Rodríguez-Flores LE, De la Fuente-Cortéz B. Cytological effects of 60 Hz magnetic fields on human lymphocytes in vitro: Sister chromatid exchanges, cell kinetics and mitotic rate. Bioelectromagnetics. 2001;**22**:145-149

[47] 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**:63-68. DOI: 10.1002/bem.10184

[48] Jacobi-Elizondo JS, Gómez-Flores R, Tamez-Guerra R, Rodríguez-Padilla C, Heredia-Rojas JA. Acute effects of 60 Hz electromagnetic fields on ex vivo murine lymphocyte and macrophage functions, and in vitro tumor cell growth. Revista Latinoamericana de Microbiología. 2001;**43**:130-134

[49] Valadez-Lira JA, Medina-Chávez NO, Orozco-Flores AA, Heredia-Rojas JA, Rodríguez-de la Fuente AO, Gomez-Flores R, Alcocer-González JM, Tamez-Guerra P. Alterations of immune parameters on *Trichoplusia ni* (Lepidoptera:Noctuidae) larvae exposed to extremely low-frequency electromagnetic fields. Environmental Entomology. 2017;**46**: 376-382. DOI: 10.1093/ee/nvx037

[50] Seyhan N, Canseven AG. In vivo effects of ELF MFs on collagen synthesis, free radical processes, natural antioxidant system, respiratory burst system, immune system activities, and electrolytes in the skin, plasma, spleen, lung, kidney, and brain tissues. Electromagnetic Biology and Medicine. 2006;**25**:291-305. DOI: 10.1080/15368370601054787

[51] Balcavage WX, Waite GN, Stéphane JP. Effects of therapeutic and low-frequency electromagnetic fields on immune and anti-inflammatory systems. In: Markov MS, editor. Electromagnetic Fields in Biology and Medicine. USA: CRC Press; 2015. p. 153

[52] Rodríguez-de la Fuente AO, Alcocer-González JM, Heredia-Rojas JA, Balderas-Candanosa I, Rodríguez-Flores LE, Rodríguez-Padilla C, Taméz-Guerra RS. Effect of 60 Hz electromagnetic fields on the activity of hsp70 promoter: An in vitro study. Cell Biology International. 2009;**33**:419-423. DOI: 10.1016/j.cellbi.2008.09.014

[53] Heredia Rojas JA, Rodríguez-de la Fuente AO, Alcocer-González JM, Rodríguez-Flores LE, Rodríguez-Padilla C, Santoyo-Stephano MA, Castañeda-Garza E, Taméz-Guerra RS. Effect of 60 Hz magnetic fields on the activation of hsp70 promoter in cultured INER-37 and RMA E7 cells. In Vitro Cellular & Developmental Biology. Animal. 2010;**46**:758-763. DOI: 10.1007/s11626-010-9342-y

[54] Rodríguez-de la Fuente AO, Alcocer-González JM, Heredia-Rojas JA, Rodríguez-Padilla C, Rodríguez-Flores LE, Santoyo-Stephano MA, Castañeda-Garza E, Taméz-Guerra RS. Effect of 60 Hz electromagnetic fields on the activity of hsp70 promoter: An in vivo study. Cell Biology International Reports. 2012;**19**:1-5. DOI: 10.1042/CBR20110010

[55] Rodríguez-de la Fuente AO, Heredia-Rojas JA, Alcocer-González JM, Rodríguez-Flores LE,Rodríguez-Padilla C, Taméz Guerra RS. Chapter 15: Promoter activation with

electromagnetism. In: Gould D, editor. Mammalian Synthetic Promoters. Methods in Molecular Biology. USA: Springer Science+Business Media LLC. 2017;**1651**:205-212. DOI: 10.1007/978-1-4939-7123-4_15

[56] Rodríguez-de la Fuente AO, Heredia-Rojas JA, Carranza-Rosales P, Heredia-Rodríguez O, Lozano-Garza G, Zavala-Pompa A, Rodríguez-Flores LE. Cytological effects of pulsed electromagnetic fields and static magnetic fields induced by a therapeutic device on in vivo exposed rats. African Journal of Traditional, Complementary, and Alternative Medicines. 2015;**12**:162-168. DOI: 10.21010/ajtcam.v12i6.17

[57] Heredia-Rojas JA, Beltcheva M, Rodríguez-de la Fuente AO, Heredia-Rodríguez O, Metcheva R, Rodríguez-Flores LE, Santoyo-Stephano MA, Castañeda-Garza E. Evidence of genotoxicity induced by 60 Hz magnetic fields on mice bone marrow as assessed by in vivo micronucleus test. Acta Zoologica Bulgarica. 2017;**8**:69-75

[58] Filmanowicz E, Gurney CW. Studies on erythropoiesis XVI. Response to a single dose of erythropoietin in polycythemic mouse. The Journal of Laboratory and Clinical Medicine. 1961;**57**:65-72