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Review Article

Biological Effects of Non-ionizing Electromagnetic Fields on Human Body and Biological System: A Systematic Literature Review

¹Daryoush Shahbazi-Gahruei, ²Samaneh Sadat Setayandeh, ³Fahimeh Aminolroayaei and ⁴Saghar Shahbazi-Gahruei

¹Department of Medical Physics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

²Queensland Micro and Nanotechnology Centre, Griffith University, 4111 Nathan, Brisbane, Australia

³Department of Medical Physics, School of Allied Medicine, Kashan University of Medical Sciences, Kashan, Iran

⁴School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

The effects of EMFs exposure on the biological systems and human body, due to its potential health hazards, have become the focus of interest since many years ago. The aim of this review is to investigate the biological effects of non-ionizing electromagnetic fields (EMFs) on human body and biological systems on the basis of recent findings. In the recent years, application of electrical devices as an artificial source of EMFs has drastically increased the amount of human exposure in daily life. In addition, protection questions and biological effects are among growing concerns which have remained largely unanswered. Among of the different spectra of EMFs, long waves or low energies EMFs named non-ionizing can influence cells process and cells proliferation. Overall, in the literature the biological effects of this kind of EMFs is a main challenge and is controversy among researchers. It was suggested that more follow-up studies with larger samples are needed for the evaluation of the effects of the EMFs. These influences in some cases are therapeutic and sometimes are destructive.

Key words: Non-ionizing radiation, electromagnetic fields, cell proliferation, biological effects, health hazards

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Corresponding Author: Daryoush Shahbazi-Gahruei, Department of Medical Physics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran Tel: +98-31-37929095 Fax: +98-31-36688597

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INTRODUCTION

Interactions between electromagnetic fields (EMFs) and biological systems raise some fundamental and unanswered scientific questions. Consequently, establishing the biological effects of EMFs, in particular non-ionizing ones, remained an elusive goal to this day. Generally, non-ionizing electromagnetic fields refer to any kind of electromagnetic field that does not carry enough energy per quantum to ionize atoms or molecules¹. Instead of producing charged ions when passing through the matter, because of having sufficient energy just for excitation, it causes the movement of an electron to a higher energy state and because of not having enough energy it does not damage DNA, directly.

Considerably, various biological effects have been observed for different types of non-ionizing EMFs^{2,3}. Non-ionizing EMFs can produce non-mutagenic effects such as inciting thermal energy into biological tissues, leading to burn. Totally, in terms of potential biological effects, the non-ionizing portion of the spectrum can be subdivided into the optical EMFs portion (visible light and infrared light) where electron excitation can occur, the portion where the wavelength is smaller than the body (Microwave (MW) and higher frequency radio frequency (RF) and heating can occur via currents induced and the portion where the wavelength is much larger than the body and heating seldom occurs via currents induced (low-frequency RF, power frequencies and static fields).

Human body consists of molecules that, when subject to the effects of EMFs, are heated by rotations of polar molecules induced by EMFs. Body temperature is homeostatically controlled. This means that if the body temperature changes from normal, body takes step to control that temperature variation. If the received EMFs are enough to enhance the body temperature by more than about 5°C, which is beyond the homeostatic control of body, it will be lethal and cause death. Furthermore, in terms of heating, the parts of body which are not subject to the high levels of blood flow such as eyes are particularly vulnerable. Thus, when heat is generated through irradiation in these organs, there is no mechanism for heat dissipating which may lead to the serious health problems. Several studies suggested that potential health hazards of EMFs, in particular non-ionizing EMFs could be linked to excessive exposure to high-power densities⁴. These health hazards including cancer, cell proliferation, headache, fatigue, Parkinson and Alzheimer diseases.

In general, many researchers have reported associations between EMFs exposure and DNA damage, but many others contradict such findings. Therefore, owing to some inevitable effects from the exposure of EMFs, it is important to

investigate all reported effects of these exposures on human body in the last few years. Hence, this review article aimed to give an overall view of the biological and health effects of non-ionizing EMFs.

ELECTROMAGNETIC FIELDS

The term EMFs covers a broad spectrum of miscellaneous forms of energy, most of which have been suspected to cause ill health to human existence. Based on the energy, EMFs have been distributed into two categories: ionizing and non-ionizing. Near ultraviolet, visible light, infrared, MW, radio waves, low-frequency RF and extremely low frequency (ELF) or long wave are all example of non-ionizing EMFs. Figure 1 shows the spectrum of EMFs and also its division to non-ionizing and ionizing EMFs.

Proofs suggested that cell processes can be influenced by EMFs. The age and state of the cell can profoundly affect the EMFs bio-response. There is no evidence that direct post-transcription effects arise as a result of the exposure of EMFs. Although transcription mutations occur, no manifest disruption in routine physiological processes such as growth and division is immediately divulged. What is usually observed is a destructible perturbation followed by an adjustment by the normal homeostatic machinery of the cells. However, any feasible side effect of this destructible perturbation even after adjustment is still of argument.

BIOLOGICAL EFFECTS

Specifically, concern has been raised about any feasible link between some types of EMFs, e.g. non-ionizing ones and cancer. As mentioned before, non-ionizing EMFs do not damage DNA directly, but they may be able to impress cells in other ways. Significantly, a sundry of symptoms has been propounded as biological effects of this kind of EMFs as listed in Table 1.

When explaining other biological effects of non-ionizing EMFs, it is considerable that MW EMFs can stimulate transcription and generation of HSP (heat-shock proteins) in cells and organisms⁵⁻⁷. The HSP are heat-shock proteins that can affect cell cycle progression. When conditions are not favorable for successful cell proliferation, e.g. high level of damaged DNA, low nutrients, hypoxia, activation of viral genomes, the cell pauses in either G1, G2 or M phase of the cell cycle, such arrest provides a cell with extra time for activation of the repair, defensive or survival machinery. If a severe incompatibility of the intracellular conditions with progression through cell cycle is signaled, the apoptosis is initiated and HSP will affect the cell cycle progression.

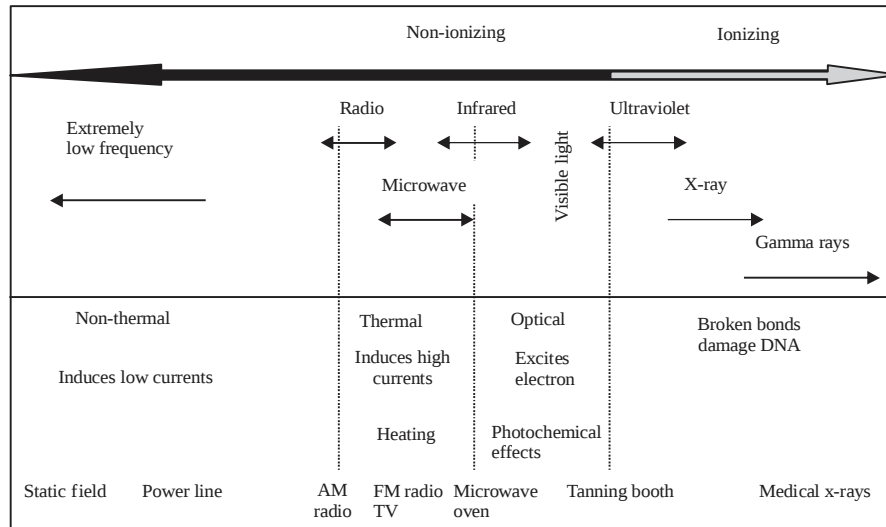


Fig. 1: Different types of EMFs (4)

Table 1: Biological effects of non-ionizing EMFs on the human health (1-10)

EMF type	Source	Wavelength	Frequency	Biological
UVA	Black light, sunlight	310-400 nm	750-950 THz	Eye-photochemical cataract, skin-erythema, inc. pigmentation
Visible light	Lasers, sunlight, fire, LEDs, light bulbs	400-780 nm	385-750 THz	Skin photoaging, eye photochemical and thermal retinal injury
IR-A	laser, remote controls	780 nm-1.4 μ m	215-385 THz	Eye-thermal retinal injury, thermal cataract, skin burn
IR-B	LASERS	1.4-3 μ m	100-215 THz	Eye-corneal burn, cataract, skin burn
IR-C	Far-infrared laser	3 μ m-1 mm	300 GHz-100 THz	Eye-corneal burn, cataract, heating of body surface
MW	PCS phones, some mobile/cell phones, Microwave ovens, cordless phones. Motion detectors, long-distance telecommunications, radar, Wi-Fi	1 mm-33 cm	1-30 GHz	Heating of body tissue
RF	Mobile/cell phones, television, FM, AM, shortwave, CB, cordless phones	33 cm-3 km	100 kHz-1 GHz	Heating of tissue, raised body temperature
ELF-RF	Power lines	>3 km	<100 kHz	Cumulation of body tissue surface, disturbance of nerve and muscle responses
Static field	Strong magnets, MRI	Infinite	0 Hz	Magnetic-vertigo/nausea, electric-charge on body

It has been shown that magnetic fields in the ELF-MF can act as a stressor in various systems. Zeni *et al.*⁸ suggested that ELF-MF and heat can act as costressors in cell cultures. They showed that ELF-MF exposure might produce a potentiated biological response such as an increase in HSPs expression, accompanying with a well-defined stress⁸.

It is noticeable that generally RF exposure will cause a change in the cell cycle and ultimately in cell proliferation. In the synchronized cells this will lead to a delay of the cell cycle which can give faulty impression that proliferation is decreased. In non-synchronized cells this will result in an apparent cell synchronization, detected as an increase in the cell proliferation. However, only when any damaged DNA is repaired, the RF generated HSP will be broken down and the normal cell cycle is resumed. It's prominent to mention that another way to resume the normal cell cycle is to dispose the cells with faulty DNA through apoptosis by the p53 activated

pathway. It's known from many cancer cell types that their p53 activity is inhibited, preventing apoptosis of faulty cells. The exposure of EMFs can deactivate the p53 apoptosis pathway. In the case of generation of HSP through oxidative stress or other stress factors, the HSP response is diminishing upon repeated exposure and so increasingly stronger stress amounts are required to obtain the same HSP response. In addition, repeated exposure to RF/EMFs can also result in proliferation of faulty cells due to failing HSP response⁸.

Investigations of the effects of RF revealed that exposure of global system mobile communication (GSM) or mobile phones 900 MHz affects the proliferation rates of human adipose-derived stem cells (ADSCs), leading to significantly lower proliferation rates in the exposed groups than the control ones, regarding the duration of exposure^{9,10}. In one of these studies, three groups of cells were irradiated for three different exposure durations ranging from 6-21 min day⁻¹,

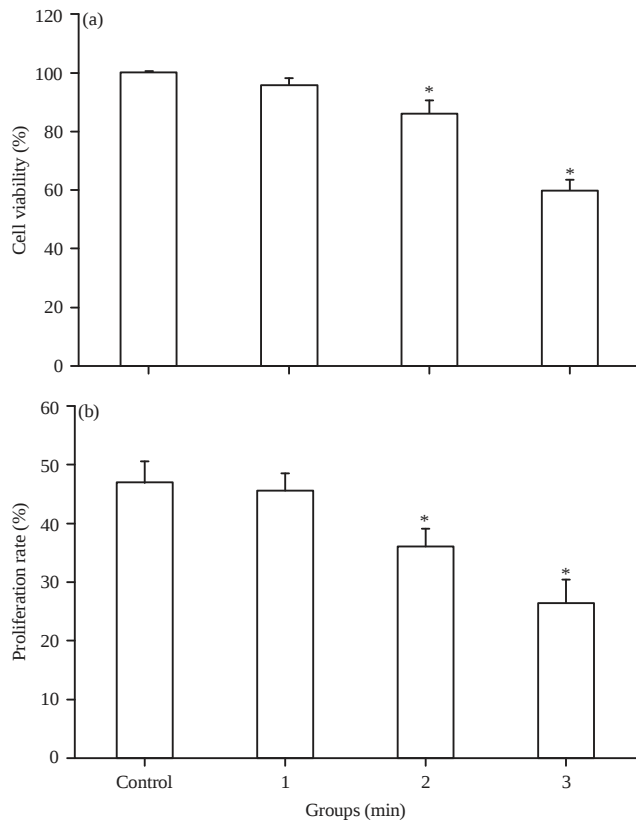


Fig.2(a-b): (a) Percentage of cell viability and (b) Proliferation rate of groups exposed to GSM 900 MHz for different daily exposure durations including control and experimental groups (6, 22 and 43 min day⁻¹)

Table 2: Values of change in proliferation rate (%) in AMA cells after RF exposure of various energy levels and exposure times (13)

Field strength (SAR/mW kg ⁻¹)	Exposure time (min)	Changes in proliferation rate (%)	
		Mean	95% confidence limit
0.021	20	-2.20*	8.1
0.021	30	-7.20	19.9
0.021	40	-11.70	21.9
0.21	20	-1.75*	11.1
0.21	30	-9.30	19.1
0.21	40	-4.80*	28.9
2.1	20	1.30*	12.6
2.1	30	-5.50	10.8
2.1	40	-10.30	14.8

*Not significant p>0.5 (paired test)

during 5 consecutive days. Group 1 was irradiated for 6 min day⁻¹. Group 2 was firstly under irradiation for 6 min and then stopped for 10 min and exposed for 16 min day⁻¹ and group 3 was irradiated for 6, 16 and 21 min day⁻¹. A dramatic decrease of cell proliferation was observed in all exposed groups, in comparison with the control one, after 5 day

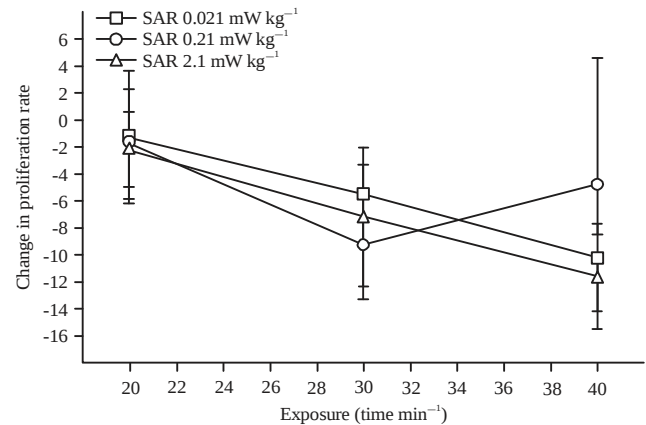


Fig. 3: Changes in cell growth after exposure to 960 MHz RF fields (13)

irradiation (*p<0.05), as shown in Fig. 2a. Moreover, ADSCs was significantly lower in all exposure groups than control one (p<0.05), except in group 6 min day⁻¹ as shown in Fig. 2b. According to the findings of this study, the proliferation rates of human ADSCs may be inhibited by exposure of GSM mobile phone 900 MHz, with intensity of 354.6 $\mu\text{W cm}^{-2}$ five times at 20 cm distance.

Furthermore, the role of GSM 900 MHz exposure in brain cancer development was reported by Leszczynski *et al.*¹¹. In this study, any feasible stress activation by GSM 900 MHz exposure to the cultures of the human endothelial cell line EA.hy 926 was investigated. It was found that GSM 900 MHz exposure to EA.hy926 cells changed the phosphorylation status of numerous proteins, e.g. heat shock protein-27 (hsp27).

Al-Serori *et al.*¹² investigated the effects of the universal mobile telecommunications system radiofrequency (UMTS-RF) signal on micronucleus (MN) formation and other anomalies such as nuclear buds (NBUDs) and nucleoplasmatic bridges (NPBs). These results indicated that the UMTS-RF signal does not cause chromosomal damage in glioblastoma cells and also suggested that the mechanisms of induction cell death needs more investigations.

More effects of RF-EMFs on biological processes such as cell proliferation was reported, exposing the cultures of transformed human epithelial amnion cells (AMA) to 960 MHz RF fields at three different power levels and exposure times¹³. Table 2 shows the changes in cell growth after RF exposure of different strength and exposure times.

A significant decrease was found in cell growth of the exposed cells, in comparison to the control ones, at all various specific absorption rate (SAR) levels, as shown in Fig. 3¹³.

However, in spite of all aforementioned biological effects of RF exposure, no direct DNA and chromosomal damages were reported, in human blood leukocytes and lymphocytes, by GSM 900 MHz exposure at low levels SAR (0.3 and 1 W kg⁻¹)¹⁴.

Since changes in cell membrane potential produce a variable electric field which plays a prominent role in cell division, so investigation of EMFs effects with similar intensity and frequency proportion to cell membrane field, i.e. ELF-EMFs, seems prominent. Due to this purpose, the effect of ELF-EMFs exposure of 50 Hz frequency, on the mechanism of cell activation in human cells, was investigated¹⁵. In this study, forty five minute exposure of monocytes to 1 µT ELF-RF revealed dramatic increases in production of superoxide radical anion and in ROS release, up-to 1.4 and 1.2 fold, respectively. They reported an increase of 4.5 fold observed in monocytes, whereas Mono Mac 6 cells had a 3 fold increase, using an intracellular activator (PMA) for production of superoxide radical anion. No more effects were detected in monocytes after co-exposure to ELF-RF/PMA, while a dramatic increase of 3.8 fold in production of superoxide radical anion was detected in Mono Mac 6 cells after co-exposure to ELF-RF/PMA compared to PMA alone.

More investigation of the effects of ELF-EMFs on the free radical production revealed a significant increase of free radical production after exposure to 50 Hz ELF-EMFs at a flux density of 1 MT, in mouse bone marrow-derived (MBM) promonocytes and macrophages¹⁶. It was found mainly superoxide anion radicals were produced after ELF-EMF exposure, both in MBM macrophages and their precursor cells, with the values of 33 and 24%, respectively. Moreover, an application of diphenyleneiodonium chloride (DPI) did not inhibit MF-induced free radical production, whereas a diminish of about 70% was observed in tetradecanoylphorbolacetate (TPA)-induced free radical production. Since no inhibitory effect was induced by DPI in MF-exposed MBM cells, it was suggested that 50 Hz ELE-EMF stimulates NADH-oxidase pathway to produce superoxide anion radicals¹⁶.

In addition, the effects of ELF-EMF on proliferation rate of ADSCs was investigated In some surveys^{17,18}. In these

studies, 50 Hz ELF-EMF with intensities of 0.5 and 1 mT was exposed to the specimens, in 20 and 40 min day⁻¹ for 7 days and cell proliferation rate was assessed. It was found that the proliferation rate of ADSCs rose significantly by ELF-EMF, according to the exposure duration. Totally, this rate in magnetic field of 0.5 mT was more than that in 1 mT¹⁷.

Results could approve the effect of ELF-EMF on cancer induction if considering the probability of DNA strand breaks, simultaneously. Furthermore, it was found that exposure of ELF-EMF can obstruct the effect of growth inhibitors hormones and help breast cancer developing^{17,18}.

Generally, one of the prominent component in assessing potential cancer risk due to the exposure of ELF-EMFs is concerning any feasible genotoxic effects of ELF-EMFs¹⁹. In order to investigate these effects, human diploid fibroblasts were irradiated to continuous/intermittent ELF-EMFs (50 Hz, 1000 µT) for 24 h, in a study. Alkaline and neutral comet assays were applied for assessing any possible genotoxic effects in form of DNA single, i.e. SSB and double-strand breaks, i.e. DSB. A dramatic rise in DNA strand break levels, mainly DSBs, was reported as compared to non-exposed controls, when applying intermittent ELF-EMFs exposure in contrast to continuous ones. The results of this study strongly revealed a genotoxic potential of intermittent EMF, indicating the potential cancer risk due to the exposure of ELF-EMFs¹⁹.

Another prominent basis for assessing the potential cancer risk due to ELF-EMF exposure is considering any possible effect of ELF-EMFs on human cells at the chromosomal level²⁰. Due to this purpose, the effect of intermittent ELF-EMFs (50 Hz, sinusoidal, 5_field-on/10_field-off, 1 mT) on the induction of micronuclei (MN) and chromosomal aberrations in cultured human fibroblasts was investigated. A time-dependent increase in MN was observed by ELF-EMF exposure, becoming significant after 10 h of intermittent irradiation at a flux density of 1 mT. A constant level of MN was detected, after 15 h exposure, approximately. In addition, an increase was seen in chromosomal aberrations, up to 10-folds above basal levels. The obtained results, as shown in Table 3 and Fig. 4, revealed a clastogenic potential of intermittent ELF-EMFs, which may lead to significant chromosomal damage in cell division²⁰.

Table 3: Values of chromosomal aberrations (%) induced by ELF-EMF exposure (50 Hz, 5_field-on/10_field-off, 1 mT) in cultured human fibroblast (20)

Type of aberrations	ELF-exposed (%±SD)	Sham-exposed (%±SD)	p-value ^b
Chromosome gaps	23.4±1.00	5.50±0.70	<0.001
Chromosome breaks	2.2±0.30	1.30±0.30	0.0015
Ring chromosomes	0.1±0.07	-	0.0113
Dicentric chromosomes	0.4±0.10	0.06±0.05	<0.001
Acentric chromosomes	0.3±0.07	0.02±0.04	<0.001

^aA number of 1000 metaphases were scored in each of five independent experiments. Results are expressed as percentage chromosomal aberrations per cell.

^bSignificant differences (p<0.05) as compared to sham-exposed controls using students t-test for independent samples

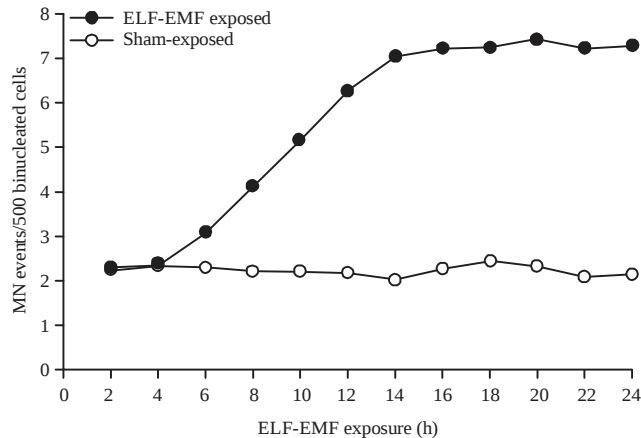


Fig. 4: Changes in values of micronuclei (MN) events induced by 2-24 h ELF-EMF exposure (50 Hz sinusoidal, 5 min-on/10 min-off, 1 mT) (20)

Table 4: Values of cortical thickness of tibial bone, in unexposed and exposed groups (23)

Unexposed (n = 8)	Exposed (n = 10)	p-value
333 ± 2.54	571 ± 6.89	<0.002

P, Unexposed vs exposed

Furthermore, a significant change in the cell growth was detected by ELF-EMFs exposure, e.g. powerlines, revealing a definitely connection between leukaemia in children and exposure to such fields²¹.

However, in spite of the potential cancer risk reported due to the exposure of ELF-EMFs, there is still some inconsistent results published in the literature, claiming low association of ELF-EMFs exposure to the cancer risk²². They showed that experiment setup can lead to obtain various conclusions related to the role of ELF-EMFs exposure in cancer disease.

In spite of all aforementioned health hazards of EMFs, the use of EMFs has been a promising candidate for better treatment of some diseases like osteoporosis, in a study²³. In this study, the preventive effects of ELF-EMFs (50 Hz, 1 μ T) on bone loss was investigated, in ovariectomized rats. The mineralization and morphology of the tibia were examined in both control and exposed specimens. An increase was also detected in the cortical thickness of the tibia, by exposing ELF-EMFs rats ($p < 0.002$), as shown in Table 4.

Furthermore, some significant increases were observed in Na and K levels in the tibia, after ELF-EMFs exposure. Moreover, an increased blood alkaline phosphatase (ALP) level was observed in exposed groups²³. In this study, application of ELF-EMFs as an effective treatment method was suggested for osteoporosis and other abnormalities related to bone loss.

More positive effects of EMFs exposure in disease treatment was illustrated in further investigation²⁴. In this

study, the effects of continuous ELF-EMFs (10 Hz, 690-720 μ T) on the level of 5-hydroxyindoleacetic acid (5-HIAA) was investigated. The specimens used in this study were adult male Wistar rats, exposing to the ELF-EMF for 15 successive days, one and three hour/s daily. Obtained results illustrated no effectiveness of ELF-EMF exposure in altering the level of 5-HIAA for 1 h daily exposure. However, it was seen that three hours daily exposure of ELF-EMF decreased the level of the 5-HIAA in the raphe nucleus, concluding its effects on the serotonergic system which may be used as a treatment of nervous system diseases, e.g. depression²⁴.

Another promising effect of EMFs in disease treatment was illustrated in further study²⁵. In this study, the effects of ELF-EMFs (125 kHz, 1.00/1.75/ 2.50 μ T), on viability and proliferation ability of MCF-7 cancer cells were investigated. Cells viability and proliferation were examined, via application of MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazoliumbromide] assay. A reduction in relative frequency of cell proliferation rate was reported, while increasing of ELF-EMFs exposure time and intensity. However, relative frequency of cell proliferation rate did not notably change with ELF-EMFs frequency increasing. According to the obtained results, division cycle of MCF-7 cells can be disturbed by application of ELF-EMFs with frequency and intensity in this range.

As it is clear, in the last two decades, the use of cellular phones has increased enormously all over the world. In this regard, a lot of works were performed on the biological effects of mobile phone in the human body. Until now, the controversy regarding whether RF fields exert effects upon biological systems is a concern for the general population. An evaluation is made of DNA damage and cytokinetic defects, proliferative potential and cell death because of RF EMFs emitted by mobile phones in healthy young users by Ros-Llor *et al.*²⁶.

Their study was carried out in 50 Caucasian mobile phone users. They collected two cell samples from each subject (a total of 100 cell samples). Ros-Llor *et al.*²⁶ reported that no statistically significant changes were recorded in relation to age, gender, body mass index, or smoking status.

Furthermore, to test whether mobile phone-associated EMF exposure affects the micronuclei (MN) frequency in exfoliated buccal cells, De Oliveira *et al.*²⁷ obtained cells smears from the left and right inner cheeks of healthy mobile phone users. MN frequencies were tested for potential confounding factors and for duration of phone use and preferential side of mobile phone use. They found no relationship was observed between MN frequency and duration of mobile phone use in daily calls. Also, these results

suggested that mobile phone-associated EMFs do not induce MN formation in buccal cells at the observed exposure levels.

Researchers³ worked on the effects of Base Transceiver Station (BTS) antennae exposure and human health. Suggested that cellular phone BTS antenna should not be sited closer than 300 m to populations to minimize the exposure of neighbors and also to reduce BTS bioeffects²⁸.

Researchers have used several different parameters to evaluate the biological and health effects of non-ionizing EMFs. The data were reported in many of publications and review articles by the international and national expert groups of scientists. All collected data was depended on both the type of study design and the methodology which reported results²⁹.

It is generally accepted that non-ionizing EMFs do not transfer enough energy to cells in sufficient amounts to cause direct DNA damage and subsequent genotoxic effects. However, it's possible that certain cellular processes, such as DNA repair, are altered by exposure to these EMFs, indirectly affecting the structure of DNA, causing strand breaks and other chromosomal aberrations, including sister chromatid exchange, or micronucleus formation³⁰. Noticeably, chromosomal damage induced by these exposures was found in some, but not all of the cell types (e.g. lymphocytes was not affected), after intermittent but not after continuous exposure. Flux density, frequency and exposure time were important for observed effects, as well as the age of the cell donors¹⁴. However, some inconsistent results regarding DNA damage induced by non-ionizing EMFs (alone or in combination with chemical or other physical agents) were reported. Consequently, a general conclusion cannot be made, regarding the overall potency for non-ionizing EMFs to participate in the carcinogenic process.

Due to different effects of non-ionizing EMFs, their protection are a major goal of scientists and organizations. For this reason, instead of the International Radiation Protection Association (IRPA), the International Commission on Non-Ionizing Radiation Protection (ICNIRP) has been established to recommend laws and protocols regarding its health effects and protections.

CONCLUSION

Recently, application of electrical devices as an artificial source of EMFs has drastically increased the amount of human exposure in daily life. Among of the different spectra of EMFs, long waves or low energies EMFs named non-ionizing EMFs can influence cells process and cells proliferation. In this

review article an overall view of the effects of non-ionizing EMFs on the human body and biological systems is presented. Overall, in the literature the biological effects of this kind of EMFs is a main challenge and is controversy among researchers.

According to lots of studies, non-ionizing EMFs affect membrane-associated events, causing changes in radical homeostasis, leading to down-stream events that include changes in gene expression, which could be of importance for regulation of proliferation. Furthermore, the effects of EMFs on biological systems, e.g. the nervous and neurotransmitter systems were reported, due to the electrical nature of them. These influences in some cases are therapeutic and sometimes are destructive.

It was suggested that more follow-up studies with larger samples in are needed for the evaluation of the effects of the EMFs. These influences in some cases are therapeutic and sometimes are destructive.

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