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SPECIAL ARTICLE

BIOLOGICAL EFFECTS OF ELECTROMAGNETIC FIELDS

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Nowadays, concerns about hazards from electromagnetic fields represent an alarming source for human lives in technologically developed countries. We are surrounded by electromagnetic fields everywhere we spend our working hours, rest or recreational activities. The aim of this review is to summarize the biological effects due to these fields arising from power and transmission lines, electrical cable splices, electronic devices inside our homes and work-places, distribution networks and associated devices such as cellular telephones and wireless communication tower, etc. Special care has been reserved to study the biological effects of electromagnetic fields on cell lines of the mammalian immune system about which our research group has been working for several years.

During the past two decades there has been increasing concern on the possible adverse health effects related to exposure to electromagnetic fields (EMF), such as immune system damage and elevation in the incidence of cancer. Actually, the presence of these fields is becoming ubiquitous in the environment, research, industry, and medicine.

Many international committees have been created to settle some standards for the siting criteria about the installation, distribution and use of power systems, for consumer electronics, mobile phones and their base stations in living areas. Experimental evidence is growing for response to static and time-varying electromagnetic fields at both the tissue and cellular levels, although the suggestion that these fields may affect biological systems has stirred considerable controversy. In fact, there are no definite and widely accepted results from laboratory or epidemiological studies, which could point out that EMF exposure can cause adverse health hazards (1-4). The crucial issue of the epidemiological findings is the lack of the identification of a biologically convincing mechanism through which these fields can condition the development or progression of tumors. Actually, the major problem is to elucidate the molecular substrates of EMF interaction and the consequent cascade of electrical and biochemical reactions that lead to a cellular and tissue response (5-7).

When evaluating whether there might be a connection between biological effects, suggestive of possible health hazards, and an electromagnetic source, it is necessary to consider the different regions of the electromagnetic spectrum. The nature of the interaction with the biological material is actually strictly dependent on the frequency or the wavelength of the source. In fact, attention has been primarily focused on extremely low frequency (ELF) or power frequency fields (50 and 60 Hz), that is a small portion of the electromagnetic spectrum. Nevertheless, basic research must be extended to the whole spectrum, in order to evaluate possible key biological markers and mechanisms relative to the different frequency fields.

It is therefore important to directly relate irradiation and unintended indirect effects in order to prevent them adequately by establishing threshold field parameters above which predictable health hazards occur (8).

In these studies we summarize the background

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information on electromagnetic fields in terms of quantities and units (see appendix), explanation of fields used in research, biological effects due to these fields arising from power and transmission lines, electrical cable splices, electronic devices inside our homes and work-places, distribution networks and associated devices such as cellular telephones and wireless communication tower.

INFORMATION ABOUT THE FIELDS

Static fields

Occupational and environmental exposure to static magnetic fields is largely due to the earth's field. It typically ranges between 30 and 70 μT, depending on location. The fields generated natually by living cells are much smaller than 0.001 μT. Static magnetic field of 20 μT can be found under direct current (DC) transmission lines. Higher static magnetic field exposures come from magnetic resonance imaging (MRI) systems, where subjects are generally exposed to static magnetic fields ranging from 0.15-2.0 T. More intense fields are used in advanced MRI units for fundamental and clinical research.

Small artificial sources of static fields are available in common devices such as audio equipment, battery-operated motors, microwave ovens. These permanent magnets produce such low field intensities as 10^3-10^4 μT within a cm of their magnetic poles.

Other sources of exposure to static fields concern personnel working in places with particle accelerators in plants using electrolytic cells.

Extremely low frequency fields

Extremely low frequency fields (ELF) deal with frequencies ranging up to 300 Hz. The predominant and commonly used frequency is 50/60 Hz. For a review of a some magnetic fields generated by common household and office appliances see ref. (9).

The electric and the magnetic components are independently measurable. The size of the exposed objects can be neglected with respect to the wavelength radiation. A useful consideration is based on the fact that, in the interaction with biological tissues, these fields have both long wavelength and skin depth. Consequently, independent, quasistatic electric and magnetic components of the fields are considered (10-11). Another important feature is that they are characterized by extremely small energy if compared to the averaged thermal energy (more than 10 orders of magnitude weaker than the latter and still smaller than the energy required to disrupt chemical bonds in a biological molecule). Tissue heating is not the origin of the biological sensitivities in these cases, and this consideration points out the non-thermal nature of the interaction. The highest field in tissue that can be induced by an ELF applied through air is about 1V/m. This implies a SAR value of 10^{-4} W/kg that is four orders of magnitude less than the body's basal metabolic rate and gives a rate of temperature of the order of 10^{-8} °C/s (11).

We can have residential and environmental exposure, or occupational exposure, depending on the source location. A special concern is devoted to the occupational places, including offices and schools, for they can involve exposures for long periods of time due to the use of household electric appliances, computers, etc. Domestic appliances can have fields of over 150 μT and 200 V/m at a distance of few cm, but these fields decrease rapidly with distance. Highest values can be found with appliances provided with high currents or high-speed electric motors. Although electric clocks and cloch radios have been considered as potential source of night-time exposure, they in fact feature magnetic fields ranging between 0.04 and 0.06 μT at 50 cm.

The environmental exposure is predominantly dominated by power and transmission lines. In their proximity, the electric and magnetic fields can join values up to about 10 KV/m and 100 μT (12).

Some occupational exposures can be in excess of 100 μT and 5.000 V/m such as in arc welders and electrical cable splicers.

High frequency RF and MW fields (300 Hz $< \nu \leq$ 300 GHz)

The major source of exposure is related to all distribution networks and associated devices such as cellular telephones and wireless communication tower, and satellite communication systems. The density power values are of the order of few tens of μW/m^2.

Current mobile phone systems operate at

frequencies between 800 and 1800 MHz. A useful consideration is worthwhile regarding the power absorbed by the user's body from the handset antenna. The highest RF exposure is localized to the head of the user. However, international guidelines have been settled to limit this localized exposure. In the workplace, RF sources are due to industrial processes, medical equipment, and all telecommunication devices. Environmental exposure is caused by radio, radar and TV broadcasting, mobile telephone base stations.

BIOLOGICAL EFFECTS

In the presence of EMF, electric charges and currents in biological tissues undergo an interaction with the field forces. Time-varying fields produce eddy currents, which are able to stimulate excitable tissues at low frequencies. Magnetic brain stimulation, for instance, may be realized by this effect. The phenomena involved may vary owing to the strength and frequency of the fields, as well as to the different characteristics of the tissue under investigation. It is therefore convenient to classify biological effects induced by EMF into two categories. A different investigative approach is actually required if we are in the presence of time-varying magnetic fields, or DC magnetic fields.

In addition, there may be a biological effect because of morphological or functional alterations following EMF exposure, but it may not result in an adverse health effect thanks to physiological repair mechanisms.

Static EMF

Electrical fields are easily shielded. The only health hazard is represented by potential electric discharge in the presence of high static fields.

By contrast, magnetic field shielding are generally expensive and require considerable engineering techniques. They can highly penetrate buildings and the body without being attenuated. Therefore, when considering any biological effects from exposure to static fields, these are essentially due to the magnetic component of the field or to the electric field and to the currents they induce in the body.

A possible effect associated with high values of static magnetic field is in an enhanced T-wave in the electrocardiograph tracing (13). This magnetohydrodynamic effect due to the field on blood flow produces a voltage across the vessel. As known, the Lorentz force is associated with the interaction of a homogeneous magnetic field with an electric charge moving with a constant velocity **v**

$$\mathbf{F}_B = q\,(\mathbf{v} \times \mathbf{B})$$

where x denotes the vector product. $\mathbf{F}_B$ is perpendicular to both the directions of **v** and **B.**

Blood, seen as a solution containing various ionic species, is characterized by an electrical conductivity, σ. Therefore, flowing blood in a vessel behaves like an electric current in a conductor of a given cross-sectional area. Reminding the definition of the current density **j** and its relation with σ, the following expression holds

$$\mathbf{j} = \sigma\,(\mathbf{v} \times \mathbf{B}).$$

j in turn undergoes a force **f** because of the presence of **B** given by

$$\mathbf{f} = \mathbf{j} \times \mathbf{B} = \sigma\,(\mathbf{v} \times \mathbf{B}) \times \mathbf{B}$$

that is responsible of a reduction in the blood flow.

In addition, an induced electric potential is provided by blood flow within the vessel of a diameter d

$$\Delta V = v\,B\,d\,\sin\alpha$$

where α is the angle between the direction of the blood flow and the magnetic field.

As shown, ΔV is v-dependent. Therefore, the largest induced voltage occurs during the T-wave portion of the cardiac cycle that is that part of the cycle characterized by the highest blood flow velocity (14).

MRI instrumentations imply exposure to static fields of high intensity, but investigations have not pointed out any relevant biological effect up to 2.0 T (13).

Extremely low frequency EMF

There is no general agreement among the reports on health risks from exposure to ELF,

although many results from the literature suggest a causal association. We can distinguish the different types of effects produced:

a) endocrine alterations
b) immune system damage
c) carcinogenic effects

Relative to a) there have been reported variations in the synthesis of pineal melatonine (15, 16).

Laboratory studies have evidenced changes in excitable tissues and neuroendocrine alterations in response to these fields that can induce voltage gradients in tissues up to 10 mV/m (17) (including evoked brain potentials and heart rate).

At the cellular level a wide variety of variations in cell structural and functional properties have been reported, such as growth rate, gene expression and macromolecular synthesis (18,19). Sspecial attention has been devoted to changes in chemical reaction rates that can alter the production of a biological substance. Results have been reported regarding changes in Ca^{++} binding to anionic fixed charges at the cell surface and changes in the transport of ions through membranes.

Findings have been reported on the ability of these fields to enhance genotoxic damage produced by known chemical carcinogens.

Epidemiological studies have evidenced a causality between a prolonged exposure to low intensity fields (> 0,3 μT) and an increase in tumors of the nervous systems, and lymphomas (20,21).

High frequency RF and MW fields

The major sources of high frequency fields are mobile telephone, microwave ovens, video terminals, TV broadcasting systems. As already mentioned, the photon energy is a factor of 10^{10} smaller tha that needed to break even the weakest chemical bond.

The EMF can exert torque on molecules thus provoking displacements of ions from unperturbed positions, reorientation of dipolar molecules such as water. Nevertheless, two considerations are required in describing the effects of low-level fields. They are the thermal noise and the kinetics of the system. In fact, the polarization effect is contrasted by random thermal agitation, and the response time of the system must be fast enough to allow it to respond with the time of the interaction. High frequency fields (above 100 kHz) can lead to a significant absorption of energy and temperature decreases. The deposition and distribution of energy within the irradiated biosystem can be assessed by dosimetric measurements and calculation. The density power or, equivalently, the SAR values depend on the incident field parameters and on the characteristics of the exposed medium. These can be its size, geometry and dielectric properties, as well as its orientation with respect to the electric field vector. From theoretical models and laboratory measurements on animals, it is possible to extrapolate average SAR distribution values (22-25). In this regard, FDTD (Finite Difference Time Domain) method (26) specifically estimates RF exposure from cellular phones.

Human absorption features a frequency-dependence. In particular, the amount of absorbed energy reaches its maximal values in correspondence of given resonance frequencies. The resonant absorption, on the other hand, goes inversely with the body size.

Thermally induced effects are among the produced bioeffects. Tissues generally and gradually restore their normal state after the heating has ceased. Tissue damage can be expected when the amount of absorbed power equals or exceeds the amount of heat generated by physiological body processes. In fact, thermally induced effects are associated also with very low average absorbed power. The "microwave hearing" phenomenon has been observed, consisting in auditory sensations experienced when the head of a person is exposed to pulsed microwaves (for instance, those generated by radars).

Many investigations have been performed on cell phone use and a growing incidence of cancer. So far, the epidemiological evidence for an association between RF radiation and cancer is found to be weak and inconsistent (27, 28).

Effects on mammalian cells

Mononuclear cell mitogen activation and stimulation is a good and valid model for the study of *in vitro* blastogenesis, proliferation, transcription and translation of many proteins (29-38). When lymphocytes are activated, they release many cytokines, chemokines and other immunological mediators (39-48). Eighteen years ago our

experimental work had shown that blastogenesis of human lymphocytes stimulated with mitogenic lectins was strongly inhibited by exposure to ELF (49-50) These effects appear to be frequency and calcium-dependent (51) Probably both the excesses and deficiencies of Ca^{2+} can lead to altered cellular response to stimulation and production of metabolic compounds. Again, since calcium is important in the neutrophil's response to stimulation of thromboxane B2 release in stimulated PMNs, it is possible that ELF influences TxB2 release by ionophore A23187-stimulated human PMNs in vitro (51). In addition, IL-1, as calcium ionophore A23187, provokes a rapid accumulation of intracellular calcium on neutrophils and ELF can modify calcium fluxes in this biological system (51). This effect was also confirmed by Liburdy, who found that calcium influx increased during mitogenesis-activated signal transduction in thymic monocytes may be altered by ELF at 22 mT, 60 Hz (52). With similar procedure the effect of *in vitro* exposure to extremely low frequency pulsed ELF on the proliferation of human lymphocytes from 24 young and 24 old subjects was also studied (53). The authors found that ELF pulses increase cell proliferation in lymphocytes from young and aged subjects.

Murine macrophages, spleen lymphocytes and thymic cells exposed to ELF for 24 hours *in vitro* increase apoptosis, change in intracellular Ca^{2+} and functional alterations in lymphocytes and macrophages after in vitro exposure to static magnetic fields (54). Even if the biological and physical mechanism of ELF are unknown today is generally believed that ELF modulates signal transduction pathway that regulates immune cells and might have a broad range of clinical effects (3). Nindl et al. hypothesized that ELF can be used to treat inflammatory diseases such as psoriasis and arthritis, since ELF can regulate lymphocyte proliferation through the activation of T cell receptor (TcR) (55). However, the effect of ELF on lymphocyte mitogen may depend on different parameters, such as mitogen concentrations, the intensity and frequency of ELF (49). Many authors have pointed out that the conceivable energy transfer from the ELF to the biological systems is too small to affect its behaviour in the absence of an amplification process. Linet et al. provide little evidence that living in homes characterized by high measured time-weighted average magnetic fields levels or by the highest wire-code category increases the rish of acute lymphocytic leukemia (ALL) in children (56). The biological mechanisms by which ELF can induce cellular changes is still unclear. Welleczek, et al., in accordance with our previous studies suggest that the cell membrane and Ca^{2+}-regulated activity is involved in bioactive ELF coupling to living systems (57). They propose that membrane mediated Ca^{2+} signalling processes are involved in the mediation of ELF effect on the immune system.

Recently, it has been reported that exposure to long term extremely low frequency electric and ELF from a 500 KV transmission line (60 Hz) provoked no significant differences in IL-1 or IL-2 activity in sheep during 27 months exposure period in blood samples (58). In accordance with these data, other authors, studying 20 immune parameters on mice exposed to 0.1mT, 60 Hz, for 1-105 days concluded that exposure to power-frequency fields produce inconsistent effects due to ELF (59).

60 Hz sinusoidal EMF of 0.1 to 0.2 mT lead to stimulation of human peripheral blood lymphocytes and lymphoid cell lines but have no influence on the frequency of sister chromatid exchanges and have opposite effects of mitogen mitomycin-C in terms of cell kinetics, mitotic rate and chromosomal breakage (60-61).

Looking at the epidemiological studies, taking all together, these results show weak correlations between exposure to ELF and the incidence of biological effects such as several cancers, childhood leukemias, chromosomal aberrations, etc. Since one potentially important response to ELF is the activation of proto-oncogenes in eukaryotic cells, because of the role of these genes in cell proliferation, Lacy-Hulbert et al., found no significant effect of 60 Hz ELF on gene expression mRNA from HL60 cells (62). Probably, all these negative effects are due to the low energy produced by EMFs to damage DNA. In contrast, ionizing radiation may increase incidence of cancer by promoting effect(s) on cellular transformation. Using ionizing radiation in cells exposed to continued static and power-frequency EMFs other authors found that EMFs appeared to have no significant direct effect on the micronucli of rat tracheal cell lines (44). However, an increased

frequency of binucleated cells with micronuclei was observed in cells exposed to 6 Gy of gamma rays and EMF compared with gamma irradiation-induced genomic alterations and increase the probability of neoplastic transformation (63).

Again, in human peripheral lymphocytes exposed to 50 Hz EMF also do not alter the spontaneous frequencies of sister-chromatid exchanges and chromosomal aberrations, but lead to an enhancement of the cell cycle progression in vitro (64). The influence of EMF may be different on lymphocyte subsets.

Our previous results on reduced mitogenic stimulation of human lymphocytes by ELF, are in accordance with Nindl et al., that found a 1.8 mT EMF and power frequence EMFs of 0.1 and 0.4 mT significantly inhibits DNA synthesis in Jurkat cells (65). In contrast with our studies they reported that EMF in medium inhibits (^{3}H)-thymidine uptake (65).

Several studies of EMF and cytokine production have been previously performed. Exposure of murine peritoneal exudates cells to a combined alternating electric and magnetic field frequency of 60 Hz has no effect on IL-1 production (66). Normal human fibroblasts exposed to EMFs 50 Hz at a range of flux density between 20 μT and 20 mT had no detectable effect on the rate of DNA synthesis by cells exposed for up to 30 h (67). Similar effect on proliferation were found on cultured K562 cells exposed to EMFs (50 Hz). However, these authors describe an effect of EMFs (2.5 mT for 96 h) on changes in cell-surface structure and physiology underlining that plasma membranes play an important role in this effect (68).

A 60 Hz ELF can act at the cellular level to enhance breast cell proliferation by blocking melatonin's natural oncostatin action with a mechanism that may involve modulation of signal transduction events associated with melatonon's regulation of cell growth (68).

However, many other studies were not covered in this review, such as research performed with Jurkat cells, other cell lines and peripheral blood lymphocytes other than studies presented here.

In conclusion, the use of different sources of electro-magnetic fields, have caused great contradictions in the international literature where experiments are not always reproducible, so the topic of biological responses to electromagnetic fields is viewed with great skepticism. There still is a need for further elucidation of the role of ELF in biological and medical systems.

APPENDIX

Quantities and units

Hereafter, it is convenient to keep in mind some physical quantities widely used when dealing with EMF and useful to specify restrictions on exposure to these fields.

As known, a static electric field, **E** is associated with the presence of an electric charge. Any other charge q in the vicinity of the former experiences an electric force **F**, due to the presence of **E** and proportional to the magnitude of q. The amplitude of **E** is so defined by the equation

$$\mathbf{E} = \mathbf{F}/q$$

that is, the electric force acting on a unit charge in a given point. **E** is expressed as volt/meter, V/m. An electric potential in a given point is the potential energy of a unit charge in that point. It is expressed in volt, V, in the international system of measurements, S. I.

When dealing with magnetic phenomena, we introduce the vector magnetic field, **H**. A magnetic field can exert forces on electric charges in motion (for example, an electric current in a conductor). It is usually given in ampere/meter, A/m.

Instead of **H,** the magnetic flux density **B** is generally used, which is related to **H** by the expression $\mathbf{B} = \mu\mathbf{H}$; μ, the constant of proportionality, is the magnetic permeability of the material. When considering exposure of non-ferromagnetic materials, such as biological materials, **B** and **H** can be assumed equal.

Both **E** and **B** are vector quantities, i. e. they are characterized by both magnitude and direction. **B** is measured in units of tesla, T.

The current density, J, is expressed in ampere per square meter ($A\ m^{-2}$). In a linear conductor, its mean value gives the current divided by the cross-sectional area of the conductor.

The frequency of an electromagnetic source (ν) indicates the rate at which the electric magnetic field goes through one complete oscillation (cycle). It is expressed in hertz, Hz, i. e., 1 Hz is one cycle

per second. The frequency and the wavelength are inversely proportional to one another, the proportionality constant being the light speed, c. In particular

$$\lambda = c/\nu$$

where $c = 3 \times 10^8$ m/s. The whole spectrum extends over about 10^{30} Hz. The big variety of phenomena involving electromagnetic waves is explained just on the basis of these frequency ranges. The visible area spreads itself in a small range centered around 10^{14}Hz. Very high frequencies (more than 10^{15} Hz) characterize hard UV and X-rays, with wavelengths of less than 10^{-9} m. Power-frequency fields (used in electric power systems) typically vary 50 or 60 times per second (60 Hz in North America and 50 Hz elsewhere) and have a wavelength of the order of 10^6 m. At lower frequencies (less than 10^{12} Hz), such as those characteristic of a microwave source, we find wavelengths ranging between 10^{-1} m and 10^{-3} m. By contrast, static fields, or direct current (DC) fields are not time dependent, so that they can be considered to have a zero frequency and an infinitely long wavelength. The internal body currents and the energy absorption in tissue induced by irradiation of time-varying EMF depend on the coupling mechanisms and the frequency involved.

In terms of potential biological effects the EMF can be divided into three categories according to their frequency values:

1. Static fields ($\nu = 0$ Hz);
2. Extremely low frequency field, ELF, ($0 \text{ Hz} < \nu \leq 300$ Hz);
3. Radiofrequency (RF) and microwave (MW) fields ($300 \text{ Hz} < \nu \leq 300$ GHz).
4. Higher frequency fields ($\nu > 300$ GHz).

Other physical quantities introduced for protection purpose are the power density S and the specific absorption rate, SAR. The former expresses the radiation power acting on a unit surface normally oriented to the direction of the propagation. The unit is watt per square meter, W/m^2. The SAR indicates the rate at which energy is absorbed by the unit mass. It is measured in watt/kilogram, W/Kg. It is obviously dependent on the incident field parameters and the characteristics of the exposed body.

As known, electromagnetic radiation can be described in terms of particles (photons) depending on the frequency of the source and the size of the object with which it interacts. The particle nature is particularly evident at high frequencies, and the energy per particle determines what biological effects that particle will induce, whether, for instance, it will have sufficient energy to disrupt chemical bonds and therefore to cause ionization. Radiation with λ smaller than the ultraviolet region ($\lambda > 10^{-7}$ m) have insufficient photon energies to cause ionization of the molecules of the medium; electronic excitation is then mostly involved, at least up to frequencies above infrared light. Possible bioeffects associated with MW and RF sources are the induction of electric currents, causing heating of the biological system. The efficiency of the mechanism depends on the frequency of the source and the orientation of the object being exposed. At frequency lesser than those used for broadcast AM (about 10^6 Hz, where the wavelength is much greater than the body) heating via induced currents is unlikely to occur. However, as will be pointed out later, these non-ionizing fields can induce bioeffects other than tissue heating. It is important to compare the field energy with the Boltzmann thermal energy, kT, where T indicates temperature (expressed in kelvin), k is the Boltzmann constant. At T = 310 K this energy has a value of $3 \cdot 10^{-2}$ eV ($4.8 \cdot 10^{-21}$joule). The electromagnetic energy of a photon is given by

$$\varepsilon = h\,\nu = h\,c/\lambda$$

where c, λ and ν have already been mentioned and h is the Planck constant.

Another crucial consideration to take into account when evaluating EMF effects is the position of the object relative to the source ("near-field" or "far-field" conditions).

If D indicates the size of the radiating source (the antenna), λ is the wavelength of the emitted radiation, r the distance between the source and the measuring point, we are in the far-field region when the two following expressions are satisfied:

$$r \geq \lambda \quad \text{and} \quad r \geq 2D^2/\lambda$$

When operating in this condition, the plane-wave model represents a good approximation of

the electromagnetic field propagation. The electric and the magnetic fields are related by means of Maxwell's equations:

$$\nabla \times E = - \partial (\mu_o H) / \partial t$$
$$\nabla \times H = - \partial (\varepsilon_o E) / \partial t$$

Since the electric and the magnetic fields and the power density are interconnected so that the measurement of one of them determines the other two.

The relationship between them is the following:

$$S = E^2_{eff}/\eta = \eta H^2_{eff}$$

where $\eta = 377\Omega$ is the impedance of the free space.

In the other source-object configuration, the field patterns are more complicated and it is necessary to measure both the electric as well as the magnetic component of the field. Here, the power density can't be appropriately used for protection purposes.

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