Chapter 106

Biological Correlates of Low-Level Electromagnetic-Field Exposure

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106.1 INTRODUCTION

During the last four decades or so there has been growing concern about the effects of electromagnetic radiation on biological systems. This is because of electronic devices, for communication, the air surveillance system, industry, and diagnostic and therapeutic purposes in medicine, emitting microwaves/radiofrequency (RF) waves. In view of this, the importance of the electromagnetic radiation pervading the environment is now increasingly realized. This has added to the list another pollutant in the environment (electropollution) after air, water, soil and noise. The effects are broadly classified into two: thermal and nonthermal, though the line of demarcation between the two is not very clear. While the former leads to an increase in body temperature, the latter does not. The nonthermal effects are attributed to the induced electromagnetic fields (**Figure 1**).

While the issue is still being debated, devices emitting these radiations have found their use in everyday life. These principally include mobile phones and microwave ovens, to name a few. Microwaves are emitted by mobile phones of the GSM type (global system for mobile

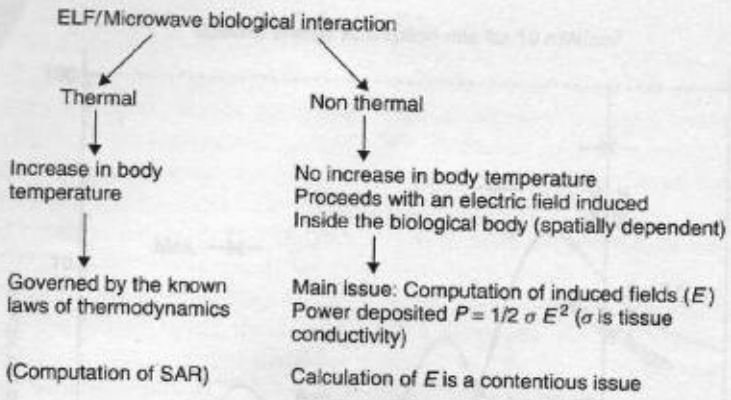

Figure 1 The boundary line between thermal and nonthermal effects is thin and not yet well defined. ELF: extremely low frequency; SAR: specific absorption rate; E_i: induced field; P: power deposited; σ: tissue conductivity.

telecommunication). It is an extremely low frequency (ELF) modulated pulsed microwave carrier. This is not the case for analogue radio and television. It can be argued that digital mobile phones transmit information in bursts of microwaves. This raises a question regarding its negative effect on human health. It has been observed that the two low-frequency sine waves (8.3 and 217 Hz, respectively) act on the composite pulsed GSM signal.

There are reports indicting adverse health effects of cell phones which emit electromagnetic radiation, with a maximum value of 50% of their energy being deposited when held close to the head. Also there is a likelihood that fields emanating from base stations (though very weak), would create a health hazard, though the issue is still being debated. It would therefore be useful to explore and understand the mechanism of electromagnetic-field effects over a wide frequency band at the existing level of RF/microwave exposure from various devices and in the environment.

While the thermal effects of microwaves are not commonly detected, nonthermal effects, if undetected, may have negative effects on human health. It is understood that RF electromagnetic fields (EMFs) from base stations to which humans are exposed (far-field exposures) are well below the allowed values. In a recent survey, it was reported that around 4% of people claim that they are sensitive to RF EMFs to some degree (Eltiti *et al.*, 2007). The biological effects also depend upon the intermittency of the exposure, may be accumulative, and may include membrane interactions that affect the ion fluxes, the modulation of neuronal impulse activity and possibly induce arrhythmia in isolated heart. Behavioural effects and those on reproductive patterns are also possible at low levels of microwave exposure. There are important biomedical considerations associated with long-term exposure to any environmental factor capable of tissue interactions. These include effects specifically attributable to wave type, duration, intermittency, frequency of recurrent exposure, interactions involving simultaneous exposure to multiple factors, age at onset of exposure and may also reflect ethnicity. While examining the biological effects, it was realized that it is not the external field, but the fields within the tissue and the body that are important.

Taking cognisance of the above, several governments have imposed limitations on the fields radiated by power systems. Biologists and the physicians have conducted many clinical tests over many years and have proposed a set of maximum values for the radiated fields, depending on the frequency.

106.2 THE PHYSICS OF THE PROBLEM

Biological bodies are inhomogeneous, having tissue-specific dielectric properties and a complex shape, making the computation of the induced field rather difficult. The fields induced inside the body depend upon, but are not limited to, the following parameters:

1. The location of the field with respect to the surroundings, for example, if there are metallic objects around, the person is grounded or otherwise
2. Polarization of the incident wave with respect to the orientation of the human body
3. Size of the human body (L) with respect to the wavelength (λ) of the incident radiation (L/λ)
4. The portion of the body
5. The electrical properties of the tissue in question.

In free-space propagation of an electromagnetic field, the power density is given by:

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

where E is the electric field strength.

Figure 2 illustrates how the average body specific absorption rate (SAR) is size and frequency dependent (free-field exposure level of 10 mW cm^{-2}, Gandhi

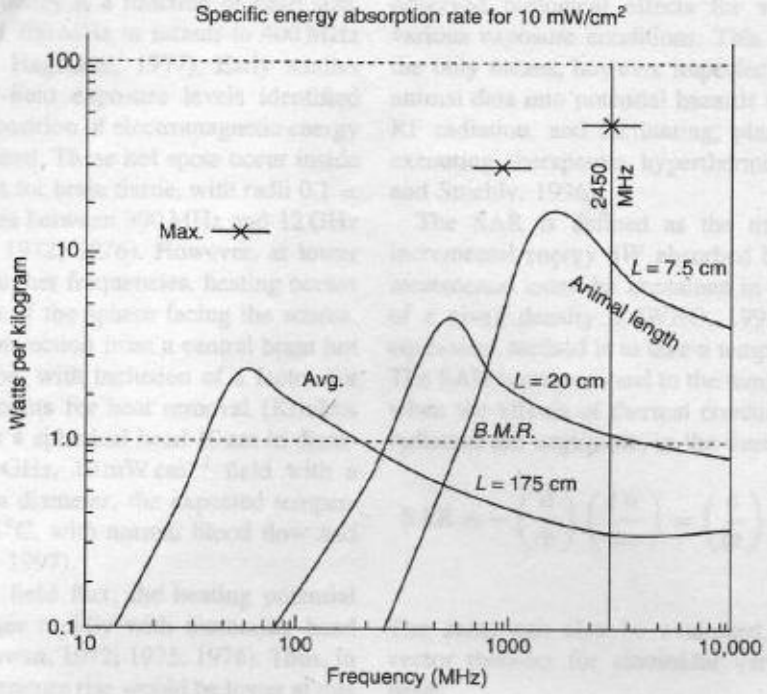

Figure 2 Average SAR in prolate spheroidal models of biological subjects exposed to electromagnetic radiation as a function of frequency. (Reproduced from Gandhi *et al.*, 1979. © IEEE.)

et al., 1979). The absorption characteristics for a prolate spheroridal model representing a man, 175 cm long, oriented parallel to an incident electric field (maximum absorption) is shown. It indicates that the average SAR, for a man model, exposed to radiation at frequencies from 10 to 10 000 MHz, first increases as the square of the frequency, reaching a peak of 2 W kg^{-1} at about 70 or 80 MHz, then gradually approaches an asymptotic value of approximately 0.16 W kg^{-1}. In the upright position, the grounded body has longitudinal resonance around 35 MHz (Gandhi and Rozzell 1975). In the transverse and anteroposterior axes, maximum absorption occurs at frequencies from 135 to 163 MHz. This configuration may be obtained in a far-field exposure. However, near-field patterns of energy absorption, as in the case of a user of a mobile phone near to the head, will be dominated by regional peaks determined by the proximity of the transmitting antenna to specific body parts and their relative orientation.

When a smaller body (simulating a rat), 20 cm long is exposed, the maximum absorption shifts towards a higher frequency, 650 MHz, and when a still smaller 7.5 cm long body (simulating a mouse) is exposed, the maximum absorption is within the microwave frequency range (2450 MHz). From simple biophysical considerations, each body therefore has a characteristic resonant frequency, depending upon the length of the long axis. Correspondingly, for the same level of incident exposure, the average value of the SAR is dependent upon the length of the body, the degree of decoupling decreasing the average value of SAR by more than an order of magnitude. It is suggestive that absorbed RF energy can be converted into other forms of energy and can cause interference with the functioning of biological systems. A significant portion of this energy is converted into heat (absorption). However, the effects are frequency dependent. At frequencies, below 100 kHz, the induced fields can even stimulate nervous tissue.

106.3 THE HEAD AS A RECIPIENT OF ELECTROMAGNETIC ENERGY

The waves falling on the biological objects may not necessarily penetrate through the entire body, but are limited to a distance determined by the skin depth. The depth to which microwaves can penetrate inside the tissue depends on the electric and magnetic properties of the tissue and of the microwave frequency. In general, at a given frequency, the lower the water content of the tissue, the greater the wave penetration and vice versa. As of now, reliable data are available on the dielectric constants of biological tissues and the assessment of biointeraction mechanisms can be quantified to an appreciable extent.

Out of all the organs, the head is the targeted recipient of electromagnetic energy from many wireless systems (e.g. mobile phones), whose impulses are also transmitted to other organs and parts. Thus, its physical and biological properties have been well investigated. For the

head, the resonant frequency is a function of head size, decreasing from around 700 MHz in infants to 400 MHz in adults (Gandhi and Hagmann, 1977). Early studies using thermalizing far-field exposure levels identified sites for preferential deposition of electromagnetic energy (hot spots) within the head. These hot spots occur inside lossy spheres, as models for brain tissue, with radii $0.1 < r > 8$ cm for frequencies between 300 MHz and 12 GHz (Kritikos and Schwan, 1972; 1976). However, at lower frequencies and much higher frequencies, heating occurs primarily at the surface of the sphere facing the source. Heat conduction and convection from a central brain hot spot have been modelled, with inclusion of a factor for blood flow, which accounts for heat removal (Kritikos and Schwan, 1979). For a spherical head 10 cm in diameter, exposed to a 1.0 GHz, 10 mW cm^{-2} field with a central hot spot 2 cm in diameter, the expected temperature rise would be 0.5 °C, with normal blood flow and heat conduction (Adey, 1997).

For a given incident field flux, the heating potential in the hot spot decreases rapidly with increasing head radius (Kritikos and Schwan, 1972; 1975; 1976). Thus, in man, the expected temperature rise would be lower at this 1.0 GHz field frequency than seen in the 10 cm model. There are strong differences in convective capacities between cerebral grey and white matters, attributable to substantially higher densities of blood-vessel capillary beds in central cortical grey matter (Ranck, 1964). For the human head, simulated as a sphere 15.0 cm in diameter with three layers representing brain, fat and skin, a 2.45 GHz (or higher frequency) field is rapidly absorbed at the surface of the head.

106.4 DOSIMETRY

At lower frequencies (<100 kHz), many biological effects are quantified in terms of current density in tissue and this parameter is most often used as a dosimetric quantity. At higher frequencies, many (but not all) interactions are due to the rate of energy deposition per unit mass. This is why the SAR is used as the dosimetric measure at these frequencies. It is expressed as W kg^{-1}. The SAR is thus the absorbed power by the absorbing mass. The most obvious approach towards dosimetric analysis is to experimentally determine the SAR distribution in phantoms simulating animal and human bodies, as well as in real cadavers. One way of determining the local or whole-body SAR is by temperature measurements. The SAR is proportional to the temperature increase only when the effects of heat diffusion can be neglected.

With these limitations in mind, the SAR concept has proven to be a simple and useful tool in quantifying the interactions of RF/microwave radiation with living systems, enabling comparison of experimentally observed biological effects for various species under various exposure conditions. This provides (as of now) the only means, however imperfect, of extrapolating the animal data into potential hazards to humans exposed to RF radiation, and facilitating, planning and effectively executing therapeutic hyperthermic treatment (Stuchly and Stuchly, 1996).

The SAR is defined as the time derivative of the incremental energy dW absorbed by or dissipated in an incremental mass dm contained in a volume element dV of a given density ρ (WHO, 1993; NCRP, 1981). An equivalent method is to take a temperature measurement. The SAR is proportional to the temperature increase ΔT, when the effects of thermal conduction, convection and radiation are negligible, in the time interval Δt.

$$\mathrm{SAR} = -\left(\frac{\mathrm{d}}{\mathrm{d}t}\right)\left(\frac{\mathrm{d}W}{\mathrm{d}m}\right) = \left(\frac{\mathrm{d}}{\mathrm{d}t}\right)\left(\frac{\mathrm{d}W}{\rho(\mathrm{d}V)}\right) = C\frac{\Delta T}{\Delta t} \tag{2}$$

The same can also be evaluated, using the Poynting vector theorem for sinusoidal varying electromagnetic fields:

$$\mathrm{SAR} = \left(\frac{\omega\varepsilon_0}{2\rho}\right) - |E_\mathrm{i}|^2 = \left(\frac{\varepsilon}{2\rho}\right) - |E_\mathrm{i}|^2 \tag{3}$$

where $|E_\mathrm{i}|^2$ is the peak value of the internal electric field (in V m^{-1}). SAR is also dependent upon if the wave type, that is, square, sine or triangular. The power of the square is larger than the other two. The average SAR is defined as the ratio of the total power absorbed in the exposed body to the mass in which it is absorbed, which is not necessarily that of the total body. The local SAR refers to the value within a defined unit volume or unit mass, which can be arbitrarily chosen.

To better understand experiments in microwave exposure, as well as their relation to safety standards; it is useful to refer to the diagram in **Figure 3**. In this diagram, with log–log coordinates of power (or power density or SAR) on the ordinate and time on the abscissa, it is possible to draw the threshold for various effects and hazards. For example, to heat a finite sample to a given temperature, the threshold is a constant SAR for long periods of time, while, for short periods of time, during which no heat is lost from the sample, the threshold curve is a line of constant specific absorption (SA = SAR − time) which is at 45° from the horizontal. The intersection of the two lines, constant SAR and constant SA, determines the applicable thermal time constant and associated 'average time' in setting exposure standards (Osepchuk and Petersen, 1996).

As evident by Equations (2) and (3), both approaches (temperature/field) have some common requirements. Any measurable field disturbance caused by the intrusion of the probe must be avoided. A further requirement is that any signal, picked by any part of the probe, other

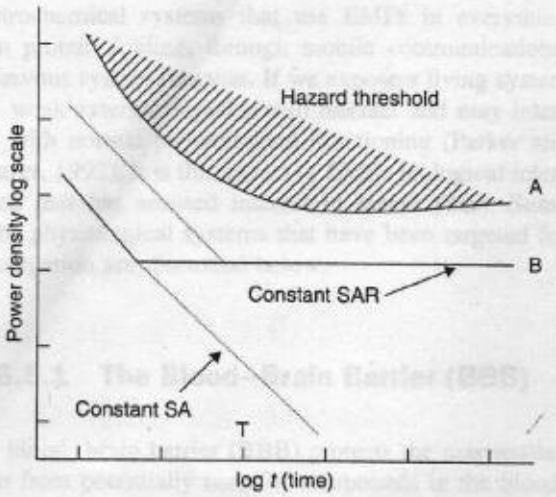

Figure 3 Thresholds for various effects and hazards expressed as a function of time. (Reproduced from Osepchuk and Petersen, 2001. © IEEE.)

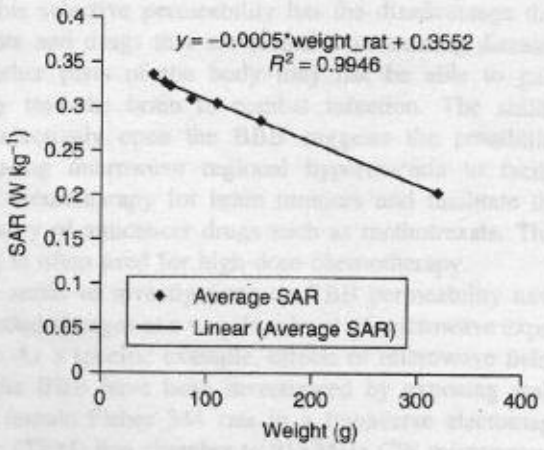

Figure 4 The linear-regression model of the SAR as a function of weight of the rat.

than the signal itself should be sufficiently suppressed. Further, the spatial resolution should be better than the smallest spatial dimension of any local field maxima or minima, in order to enable accurate assessment of the SAR distribution. Determination of the SAR distribution requires measurements in the tissue volume of interest. In larger volumes, with greatly nonuniform distributions, SAR varies from place to place, demanding measurements in several places, and the location of the sensor must be precisely known.

In animal experimentation (particularly in the developing stage) it is clear that as the animal age increases (and hence the weight) the SAR values change and dosimetric estimation becomes uncertain. On the basis of theoretical formulation from Durney *et al.* (1979), weight/age increases for the rat as shown in **Figure 4**. It is found that SAR in the foetus is strongly dependent on the geometrical relationship between the foetus and the EM source, while the average SAR for the foetus is always lower than the RF safety guidelines under the exposure conditions (Togashi and Ryder, 2007). The single-value concept of SAR thus has many uncertainties.

Also, the concept of SAR is not sufficient when one is looking for biological effects not dependent upon absorption. This raises questions about using these parameters for evaluating effects that may be of another nature. The possibility of nonthermal effects is thus a controversial one and the problem of dosimetry becomes much more complex. SAR may be a valid quantitative measure of interactions other than absorptive ones, when the mechanism is dependent on the intensity of the electric field, except, however, when the direction of the field is of importance with respect to the biological structure. Similarly, the SAR concept may not be sufficient for direct interactions with the E field. Further, there is always a level of uncertainty about perceived field strength and actual RF exposure.

The extrapolation of results from animal experiments (mostly) to humans is used in a reduced form, termed frequency scaling. The approach essentially enables us to use results from one model experiment and to predict results in another biological object, differing only by a scale factor. The frequency-scaling principle can be applied to determine the equivalence between the exposure of a man of height l_m and an animal of a length l_a, with both man and animal having the same orientation with respect to the exposure field, using the relationship:

$$f_m l_m = f_a l_a \tag{4}$$

where f_m and f_a are the frequencies at which man and animal are exposed, respectively (Durney and Christensen, 2000). It should be mentioned that the SAR distribution in the two cases will be similar in the two bodies (but may not be the same). This may be valid for low losses, which is not always be the case for biologic structures.

106.5 BIOLOGICAL EFFECTS

While considering the biological effects of electromagnetic-field exposure, the evidence for nonthermal effects has been gathered under two headings: (i) *in vitro*: altered cell responses and (ii) *in vivo*: results of chronic exposure in animals. The data available on biological effects of electromagnetic-field exposure are immense and at times contradictory. These effects may not always produce adverse health impacts. There is an element of uncertainty across various mobile frequency bands and also on whether the target under investigation is brain or muscle tissue. Living systems are

electrochemical systems that use EMFs in everything from protein folding, through mobile communications, to nervous system function. If we expose a living system to a weak external signal it will interact and may interfere with normal physiological functioning (Parker and Winters, 1992). It is this aspect of EMF–biological interaction that has aroused interest in recent years. Some of the physiological systems that have been targeted for investigation are discussed below.

106.5.1 The Blood–Brain Barrier (BBB)

The blood–brain barrier (BBB) protects the mammalian brain from potentially harmful compounds in the blood. It is a selectively permeable, hydrophobic barrier that is readily crossed by small, lipid-soluble molecules. It serves, not only to restrict entry of toxic polar molecules into the brain, but also as a regulatory system that stabilizes and optimizes the fluid environment of the brain's intracellular compartment. A dysfunctioning BBB allows influx of normally excluded hydrophilic molecules into the brain tissue. This might lead to cerebral oedema, increased intracranial pressure and, in the worst case, irreversible brain damage. Opening of the BBB may subject the central nervous system (CNS) to assault from extraneous micro-organisms. It is thus a natural defence system that maintains the physicochemical environment of the brain within certain narrow limits that are essential for life.

The BBB has thus been a subject of investigation because of its vicinity to the radiation source and its central function in the human brain. Because of its penetration, exposure of an electromagnetic field could cause significant alteration in BBB behaviour. The emission intensity of sodium fluorescein in brain tissue exposed to an EMF for 30 minutes was larger than that without such exposure (Williams *et al.*, 1984). In a study on the transport of D-mannitol across the BBB, it was observed that a higher power (larger SAR) generally yielded larger permeability, and a pulse wave was more effective in permeability enhancement than a continuous wave (CW) (Oscar and Hawkins, 1977). Further, for higher electromagnetic frequencies, the conductivity was larger, with a correspondingly higher SAR (Equation 3), hence producing a greater permeability. Larger modulation also induces greater permeability. In addition, the conductivity at a depth of 50% was larger than that for 0% for an AM (amplitude modulation) wave with a modulation of 16 Hz (Albert *et al.*, 1987). A twofold increase in the BBB permeability of sucrose was obtained after exposure to an EMF of 1.8 GHz over four days (Schirmacher *et al.*, 2000). From all these observations, it can be concluded that permeability enhancement was not because of temperature increase, as it was within the variation of 1 °C in daily rhythm.

This selective permeability has the disadvantage that agents and drugs that are effective in treating diseases in other parts of the body may not be able to gain entry into the brain to combat infection. The ability to selectively open the BBB suggests the possibility of using microwave regional hyperthermia to facilitate chemotherapy for brain tumours and facilitate the delivery of anticancer drugs such as methotrexate. This drug is often used for high-dose chemotherapy.

A series of investigations on BBB permeability have revealed changes at a very low level of microwave exposure. As a specific example, effects of microwave fields on the BBB have been investigated by exposing male and female Fisher 344 rats in a transverse electomagnetic (TEM) line chamber to 915 MHz CW microwaves, as well as pulse-modulated waves with repetition rates of 8, 16, 50 and 200 per second. The SAR varied between 0.016 and 5 W kg^{-1}. The rats were not anaesthetized during the two hours of exposure. The results show that both continuous and pulsed microwaves have the potential to open up the BBB for albumin passage, with no significant difference between the two (Salford *et al.*, 1994).

106.5.2 The Nervous System

Due to the proximity of a mobile phone to the head, most research efforts have been concentrated on estimating the potentially toxic effect of RF on the CNS. This is largely because the nervous system is the body's main control and integrating network. Its activities are divided into two parts: sensing and then responding. In the first category it serves two functions: sensing intrinsic and extrinsic (environmental) stimuli, and interpreting and integrating these signals. In the second phase, it responds to interpretation by initiating actions in the form of muscular contractions or glandular secretions. The nervous system of vertebrates is composed of two primary parts: the central nervous system composed of brain and spinal cord and the peripheral nervous system, composed of all nerves outside the CNS. When the nerves or brain are perturbed, for example by RF radiation, morphological, electrophysiological and chemical changes will take place. These include transient minor effects on a electroencephalogram (EEG), on sleep structure and on cognitive processes in human subjects (Mann *et al.*, 1997. A significant change in these can lead to a change in overall behaviour. It has been further reported that different areas of the brain have different sensitivities to RF radiation (Lai *et al.*, 1989; Ray and Behari, 1988). Exposure of the brain to a mobile phone may lead to an increase in temperature to the extent of 0.1 °C (Van Leeuwen *et al.*, 1999; Wainwright, 2000), after taking into consideration the high blood-perfusion rate.

This, in contrast to skin blood perfusion, was significantly elevated after exposure to mobile phone frequencies (Monfrecola *et al.*, 2003). Under some conditions, such as when the handset operates at full transmitter power because of a long distance to the next base station, local SAR values in the brain are reported to be in the range of $1\,W\,kg^{-1}$ or more (Huber *et al.*, 2003).

106.6 THE ROLE OF CALCIUM

106.6.1 Effects on Metabolism

Lerchl *et al.* (2008) have shown that chronic RF exposure (383, 900 and 1800 MHz) leads to frequency-dependent increase of body weight in Djungarian hamsters at moderate SAR values. These authors have concluded that this is indicative that metabolic processes may be affected by such exposures. It is possible that molecular processes involved with the brain energy metabolism of the rat may be perturbed by radiation in the microwave frequency region. It has been reported that there are divalent iron atoms and two divalent copper atoms in the molecules of the respiratory chain (Lehninger, 1965). Each of these is essential to the respiratory function at the molecular level. Charged particles like these, if not otherwise constrained, undergo translational motion in an electric field. Such a group of particles would possibly respond to an oscillating electric field over a wide range of frequencies, starting from natural RF oscillations up to the highest values to which natural process react (Sanders *et al.*, 1984). Nicotinamide adenine dinucleotide (NADH), adenosine triphosphate (ATP) and creatine phosphate (CP) are key compounds in brain energy metabolism. ATP is a key compound in energy metabolism because it is the carrier of energy for the processes in living cells. NADH is oxidized to produce ATP in the mitochondria, while brain ATP concentration is maintained at the expense of CP. When demand for ATP is higher than the mitochondrial production capacity, CP is rapidly converted to ATP to sustain ATP levels and a significant decrease in CP levels is observed prior to any decrease in ATP. The changes in these compounds are frequency dependent.

Another effect on metabolism of electromagnetic radiation is the leakage of free calcium ions, either through the cell's external membranes or those surrounding internal 'calcium stores'. This can have dramatic effects on many aspects of metabolism and explains results like the stimulation of growth and increased risk of cancer, symptoms suffered by electrosensitive humans. Calcium concentration inside the cell controls the rate of many metabolic processes, for example, the activity of many enzyme systems and the expression of genes. Ca^{+2} ions use special channels to cross the membrane along the concentration gradient. The concentration of calcium ions in the cytosol is normally kept about a thousand times lower than that outside by metabolically driven ion pumps in the membranes. Electromagnetic-field stimulation increases membrane leakiness, causing unregulated amounts of extra calcium to flood in. The actual effects depend on the programmed state of the cell at that instant of time; for example, the growth rate, the repair rate after injury or the rate of healing can be enhanced. On the other hand, if there are mutant precancerous cells present, it may also lead to tumour promotion.

106.6.2 Calcium Release from Cell Membranes

Ca^{+2} ions are able to bind without causing deformations to either membrane proteins or soluble proteins of the cytoplasm or organelles. They have several ion-binding sites and, by changing their configuration as a function of the occupied site, they are capable of exciting a specific target enzyme. The Ca^{2+} ion has been identified in relaying electrochemical messages to the cell surface and thus is the most critical target for microwave exposure. It is known that Ca^{2+} signalling has extreme sensitivity to coherent excitation by very low field energies within specific amplitude and frequency windows (Gartzke and Lange, 2002). This causes a large electrostatic force to be generated at the cell surface. The lowest level of exposure could be $0.00015\,W\,kg^{-1}$ ($0.08\,\mu W\,cm^{-2}$) with a 16 Hz signal modulated at 240 MHz (Schwartz *et al.*, 1990). The mechanism of action of gonadotrophin releasing hormone (GnRH) on the anterior pituitary gonadotrophin reveals that Ca^{2+} functions as a second messenger in the GnRH-activated signal-transduction cascade (Jennes *et al.*, 1995; Haisenleder *et al.*, 2001; Liu *et al.*, 2003).

Ca^{+2} ions use special channels to cross the membrane along the concentration gradient. These voltage-gated channels are normally closed in excitable cells, but they open in response to an action potential. There has always remained a question of whether the cell membrane (calcium ion channel), is directly involved in electromagnetic-field interactions (Liburdy, 1992). This is important because the receptor sites and ion channels are located in the cell membrane and are first involved in the signal-transduction processes. Another question is if alterations in the calcium fluxes are propagated down the signal-transduction cascade to alter events such as gene activation. Further, changes in the calcium ion second messenger are linked to induction of c-myc messenger RNA, a mid-stage signal-transduction marker, which, in turn, travels down the signal-transduction cascade to alter gene activation events and cell proliferation.

106.6.3 Brain Function and EMF Effects

The role of calcium in the control of brain function has been under investigation and was found to be influenced by a range of modulating frequency. A statistically significant increase in net $^{45}Ca^{2+}$ transport was observed for modulating frequencies of 6–16 Hz, followed by a fall over the frequency range 20–35 Hz (Bawin *et al.*, 1978). The nonlinear effect of modulated waves on chicken cerebral tissue has also been demonstrated with $^{45}Ca^{+2}$. The animals were exposed to 0.8 mW cm^{-2} at 147 MHz, amplitude modulated by a sinusoidal signal (0.5–35 Hz). The existence of frequency windows was confirmed (Blackman *et al.*, 1979) for an incident power flux of 1 mW cm^{-2}; there was a positive response when the modulation lay between 6 and 12 Hz, but little response at 0.5 and 20 Hz. A power window was also shown to exist at constant frequency; when the chicken cerebral tissue was submitted to a 450 MHz carrier wave modulated at 16 Hz there was a significant increase in power levels of 0.1 and 1 mW cm^{-2}, while no effect was observed for power levels of 0.05 and 5 mW cm^{-2}. Similar results in terms of frequency and power windows were reported by Kunjilwar and Behari (1993) who exposed rats to 112 MHz, amplitude modulated at 16 Hz (SAR 0.1 W kg^{-1}), and reported changes in acetylcholineste rase activity and Na^+/K^+ phosphatase activity (Behari *et al.*, 1998). They observed no significant changes when the CW was changed to 73.5 and 36.75 MHz with a modulating frequency of 76 Hz. The limits of the frequency and power windows were 6–20 Hz and 0.1–1 mW cm^{-2}, respectively (Gandhi, 1982). The carrier frequency was shown to be less than 1 GHz, but itself had little effect, while the modulating frequencies were more controlling. For avian brain tissue under an AM wave, conductivity at a modulation of 16 Hz was 1.2 times that for 3 Hz (Albert *et al.*, 1987). For human brain, conductivity also increases with an FM modulation increase from 9 to 16 Hz (Blackman *et al.*, 1979).

Bawin *et al.* (1975) have found that exposing brain tissue to weak VHF (very high frequency) radio signals modulated at 16 Hz released calcium ions bound to the surfaces of cells. Blackman *et al.* (1982) concluded that weak fields were often more effective than strong ones. Without these ions, cell membranes are weakened and are more likely to tear under the stresses and strains imposed by the moving cell contents. Although the resulting holes are normally self-healing, they will increase leakage while they are open and this can explain the bulk of the known biological effects of weak electromagnetic fields. Leaks in the membranes surrounding lysosomes can release digestive enzymes, including DNAse (an enzyme that destroys DNA). Panagopoulos *et al.* (2007) showed that exposing adult *Drosophila melanogaster* to a mobile phone signal for just six minutes a day for six days broke the DNA in the cells that give rise to eggs into fragments, and half of the eggs died. Diem *et al.* (2005) also found significant fragmentation after exposing cultured rat and human cells to a simulated mobile phone signal for 16 hours. They showed that exposing human cells for 24 hours to simulated phone signals gave DNA fragmentation similar to that due to the gamma rays emitted from a radioactive isotope.

106.7 ELECTROMAGNETIC-FIELD EXPOSURE AND ENZYME ACTIVATION

106.7.1 Ornithidine Decarboxylase (ODC)

Ornithidine decarboxylase (ODC) is an enzyme essential for cell growth and DNA synthesis. It is a rate-limiting enzyme in the synthesis of polyamines. Polyamines (putrescine, spermadine, spermine, cadaverine) are long-chain molecules that are positively charged (polycationic). They have the highest charge/mass ratio of any biomolecule. High ODC activity occurs in the unregulated growth of tumour cells, as in the malignancy prostate cancer (**Figure 5**).

RF exposure has been shown to induce ODC activity, levels of which are often elevated during cell growth and tumour promotion. The exposure of mouse fibroblasts to amplitude modulated microwaves at an SAR of 3 W kg^{-1} increase ODC activity (Penafield *et al.*, 1993), but to a much lower level than treatment with a chemical promoter. Litovitz *et al.* (1993) have examined the modulation frequency dependence of ODC activity in cultured cells (fibroblasts), determining the minimal duration that a single ELF modulation frequency must be sustained (coherence time) in order to elicit an ODC response. Using a 915 MHz field, switching modulation frequencies from 55 to 65 Hz at a coherence time of one second or less abolished enhancement of ODC responses, while coherence times of 10 seconds or longer produced full enhancement. These microwave coherence effects and pulsed effects are similar to those observed in ELF fields.

In an investigation in murine L929 cells, ODC was activated by an AM wave at 845 MHz, though it was not affected by frequency modulation (FM) at the same frequency (Penafield *et al.*, 1993). ODC synthesizes polyamines, which promots the permeability of superoxide dismutase (SOD) across animal cell membranes (Poduslo and Curran, 1996).

106.7.2 Protein Kinase C Activity

Protein kinase C (PKC) plays a key role in a variety of pathologic states, including oncogenesis (Harvey

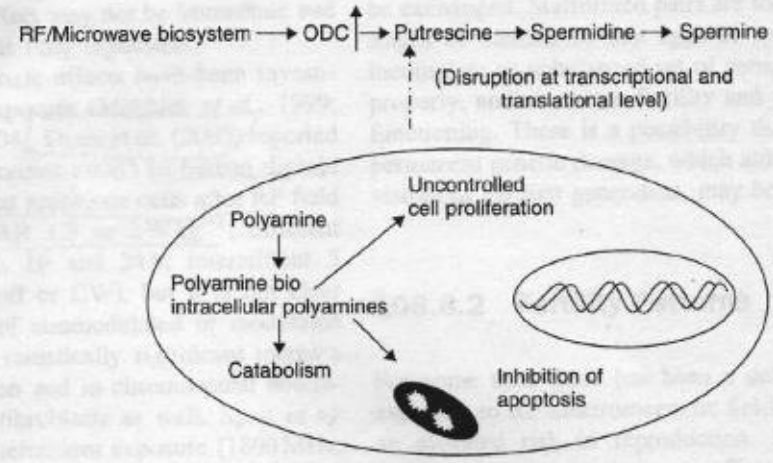

Figure 5 Mode of RF/microwave interaction with biological system in tumour promotion.

and French, 2000; Nishizuka, 1986), and in mediating cellular responses to extracellular stimuli involved in proliferation, differentiation, apoptosis and exocytotic release in a number of non-neuronal cells (Ohkusu *et al.*, 1986). Several lines of evidence suggest that PKC modulates ion conductance by phosphorylating membrane proteins such as channels, pumps and ion-exchange proteins, besides its role in extrusion of Ca^{2+} immediately after its mobilization into cytosol. The enzyme has also been implicated in phosphorylation of several neuronal proteins, which are thought to regulate neurotransmitter release and long-term potentiation in memory formation (Suzuki, 1994).

The activation of this enzyme is thought to be biochemically dependent on Ca^{2+}. Tumour-promoting phorbol esters have a structure very similar to diacylglycerol and activate protein kinase C directly, both *in vitro* and *in vivo* (Castagna *et al.*, 1982). It has been variously reported that protein kinase C is the receptor for tumour promoters (Parker *et al.*, 1984). Tumour promoters, such as phorbol esters, increase the affinity of the enzyme for Ca^{2+}, resulting in its full activation at physiological Ca^{2+} concentration. TPA has a specific membrane receptor in the cell membrane (Hunter *et al.*, 1984; Niedel *et al.*, 1983). In order to stimulate cell proliferation in cells, growth factor and PKC are needed to induce the signal pathways. Byus *et al.* (1984) reported a decrease in the activity of this enzyme following exposure of human lymphocytes for a period of 15–30 minutes to 450 MHz, amplitude modulated at 16 Hz.

106.8 GENOTOXIC EFFECTS

The photon energy of RF radiation (10^{-3}–10^{-6} eV) is much less than the energy required to break chemical bonds (hydrogen bonds ~0.5 eV) and therefore it is believed that this radiation does not damage DNA. However, it is possible that certain cellular constituents are altered by exposure to EMF, such as free radicals. Free radicals are able to interact with DNA or other cellular components and are involved in cell regulatory processes.

106.8.1 Electromagnetic Fields and DNA

- Since nerve cells do not divide and are not likely to become cancerous, more likely consequences of DNA damage in nerve cells are changes in function and cell death, which could either lead to or accelerate the development of neurodegenerative diseases.
- EMF-induced DNA damage could be blocked by treating rats with antioxidants, including melatonin, immediately before and after exposure. Melatonin is a hormone secreted from the brain's pineal gland. As a potent antioxidant, it effectively eliminates free radicals inside cells.
- The effect of RF radiation on DNA could conceivably be more significant on neurons than on other cell types, because these nerve cells have a low capability for DNA repair.

DNA damage may lead to increased mutation frequency and could be linked to gene mutations. A gene is a section of DNA containing the information needed to make a particular protein or enzyme. There is also a section that can turn the gene on or off in response to outside signals. The growth of an organism from a fertilized egg involves a hugely complex pattern of switching genes on and off that regulates growth, cell division and differentiation into specific tissues. DNA damage can sometimes give unregulated growth to form

tumours. However, the effect may not be immediate and may take years before it is fully replicated.

In most studies, genotoxic effects have been investigated after short-term exposure (Moulder *et al.*, 1999; Vijayalaxmi and Obe, 2004). Diem *et al.* (2005) reported DNA strand breaks (by comet assay) in human diploid fibroblasts and cultured rat granulose cells after RF field exposure (1800 MHz, SAR 1.2 or 2 W kg^{-1}; different modulations; duration 4, 16 and 24 h; intermittent 5 minutes on/10 minutes off or CW), but it is not clear if continuous exposure of nonmodulated or modulated 1800 MHz was used. A statistically significant increase in micronucleus formation and in chromosomal aberrations were observed in fibroblasts as well. Speit *et al.* (2007) used CW with intermittent exposure (1800 MHz, SAR 2 W kg^{-1}), applied using the same cell system and reported negative results. Nikolova *et al.* (2005) reported, after six hours, but not after 48 hours RF field exposure, a low and transient increase in DNA strand breaks in embryonic stem-cell-derived neural progenitor cells.

When mice were exposed to 2.45 GHz fields at an SAR of 1.18 W kg^{-1} for two hours per day for 120, 150 and 200 days, structural genomic rearrangement were observed in brain and testes cells (Sarkar *et al.*, 1994). Lai and Singh (1995), (1996) reported that rats exposed to pulsed (two-second pulses, 500 pulses per second) or CW 2.45 GHz fields with SARs of 0.6 or 1.2 W kg^{-1} for two hours increased the number of single- and double-strand breaks in brain cell DNA when assayed four hours after RF exposure. Lai and Singh (1997) also reported that treatment of rats immediately before or after exposure with either melatonin (1 mg kg^{-1}) or PBN (*N*-*t*-butylphenylnitrone, 100 mg kg^{-1}) blocks the formation of DNA breaks by RF fields. These experiments challenge the belief that RF fields are unable to break molecular bonds. Epigenetic events may be involved. Paulraj and Behari (2006) studied the same phenomena at other frequencies and low dose level, and confirmed DNA strand break; they also concluded that the hippocampus is the targeted site of such interactions.

While damage to DNA strands has been confirmed by several workers, it is argued that its repair is an ongoing process and the damaged chromosomes can be reconstituted. However, this proposition is not without risk. There is no guarantee that these will replicate in the manner they were originally present. Pieces may be left out (deletions), joined in backwards (inversions), swapped between different parts of the chromosome (translocations) or even attached to the wrong chromosome. The effect may also be frequency dependent. In most cases, the new arrangement can work for a while, if most of the genes are still present, and any metabolic deficiencies can often be made good by the surrounding cells. However, things may be different when it comes to meiosis. During meiosis, the chromosomes line up in pairs (one from each original parent) along their entire length so that corresponding parts are adjacent and can be exchanged. Malformed pairs are torn apart in the later stages of meiosis so that eggs or sperms that have an incomplete or unbalanced set of genes may not function properly, and so reduce fertility and other physiological functioning. There is a possibility that this may lead to permanent genetic damage, which although it may not be visible in the first generation, may be evident thereafter.

106.8.2 Fertility Patterns

For some time there has been a debate about whether exposure to RF electromagnetic fields is associated with an elevated risk in reproduction. Radio waves from mobile phones may have an effect on the process of spermatogenesis. According to one study, lifestyle can decrease semen quality (Kilgalton and Simmons, 2005) and prolonged use of mobile phones can have negative effects on sperm motility chacteristics (Fejes *et al.*, 2005). It has been shown that sperm DNA damage is not repaired, because of the chromatin structure (Singh and Stephens, 1998).

Concerns are growing about the possible hazardous effects of RF electromagnetic waves (EMW) emitted by household electronic gadgets on human health. Nakamura *et al.* (2003) found that exposure of pregnant rats to 2.45 GHz CW microwaves at 2 mW cm^{-2} power density for 90 minutes decreased uteroplacental blood flow and increased progesterone and $PGF_2\alpha$ (placental growth factor). Dasdag *et al.* (2003) reported a decrease in seminiferous tubule diameter in male rat testes after exposure. They used a commercially available 890–915 MHz global signal module with 0.141 W kg^{-1} whole-body SAR. More recently, Aitken *et al.* (2005) found significant damage to mitochondrial and nuclear genomes in epididymal spermatozoa of mice, when exposed to RF 900 MHz EMW, 12 hours a day for seven days. Several authors (Fejes *et al.*, 2005; Ji-Geng *et al.*, 2007; Kesari and Behari, 2008) have also observed that carrying the mobile phones near reproductive organs for a longer time may have negative effects on sperm motility and male fertility.

Forgacs *et al.* (2006) have reported that repeated whole-body 1800 MHz GSM-like microwave exposure (0.018–0.23 W kg^{-1}) below the maximum permissible exposure (MPE) level recommended by the International Commission for Nonionizing Radiation Protection (ICNIRP) is able to increase the serum testosterone level, RBC (red blood cells) and VPRC (volume of packed red blood cells) in male mice, although still within physiological limits. These authors further reported that the unaltered *in vitro* steroidogenic capacity of Leydig cells obtained from microwave-exposed mice suggest that Leydig cells are not the primary targets of the applied microwave exposure or the direct action is transient only and confined to the period of exposure. This suggests that

the main target of action is probably located at the higher regulation level of the hypothalamic-pituitary-gonadal axis. It is known that prolonged use of GSM mobile phones may lead to reduced melatonin production (Burch *et al.*, 2002; Jarupat *et al.*, 2003). Melatonin exerts an antigonadotrophic effect mainly at the level of the hypothalamus and pituitary (Jackson *et al.*, 1984; Bittman *et al.*, 1985; Vanecek, 1998) and directly decreases the testosterone secretion in Leydig cells too (Valladares *et al.*, 1990; Kus *et al.*, 2002).

Sun *et al.* (2005) investigated the effects of electromagnetic radiation emitted by computers on human sperm quality and did not find any adverse effects. Reactive oxygen species (ROS), such as superoxide anions ($O_2^{\bullet -}$), hydroxyl radicals ($OH^{\bullet}$) and hydrogen peroxide (H_2O_2) may influence the structural integrity and function of sperm, such as motility, capacitation and sperm–oocyte fusion (Griveau *et al.*, 1995). Spermatozoa are particularly vulnerable to oxidative stress because their plasma membrane is rich in polyunsaturated fatty acids (PUFAs) and membrane bound NADPH oxidase. ROS have been shown to correlate with reduced male fertility (Iwasaki and Gagnon, 1992), cause perioxidative damage to the sperm plasma membrane (Hughes *et al.*, 1996), and induce both DNA strand breakages and oxidative base damage in human sperm (Kodama *et al.*, 1997). A decrease in total antioxidant capacity of seminal plasma has been correlated with a reduction in sperm quality, such as concentration, motility and morphology (Smits *et al.*, 1998).

The issue that biological effects of RF radiation are genotoxic is still not fully resolved, though some of the available results do not discount such a possibility. Some *in vitro* data show effects that are negative, while others are positive, close to the guidelines levels for safe exposure.

106.9 NONGENOTOXIC EFFECTS

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

Apoptosis is an important mechanism of protection against cancer. Several studies have reported RF field effects on human peripheral blood mononuclear cells (Capri *et al.*, 2004a), lymphoblastoid cells (Marinelli *et al.*, 2004), epidermis cancer cells (Caraglia *et al.*, 2005), human Mono Mac 6 cells (Lantow *et al.*, 2006c) and Molts 4 cells (Hook *et al.*, 2004). No difference in apoptosis induction was detected between sham-exposed and RF-field-exposed cells (Hook *et al.*, 2004). On the other hand, Marinelli *et al.* (2004) have reported a better survival rate of T lymphoblastoid leukaemia cells exposed to 900 MHz nonmodulated RF fields and Caraglia *et al.* (2005) found apoptosis induction in human epidermoid cancer cells after exposure to 1.95 GHz fields. The REFLEX study (Nikolova *et al.*, 2005) reported no effects of RF fields on cell cycle, cell proliferation, cell differentiation, apoptosis induction, DNA synthesis and immune cell functionality. These authors described some effects on the transcript level of genes, after RF exposure, related to apoptosis and cell-cycle control; however, these responses were not associated with detectable changes in cell physiology. Analysis of whole-genome compementary DNA arrays show alterations in gene expression after various RF exposure conditions using different cell types, but no consistent RF signature, such as stress response, could be identified (Remondini *et al.*, 2006).

Heat-shock proteins act primarily as molecular chaperones to eliminate unfolded proteins, which can also appear from cellular stress. This stress response can be induced by many different external factors, including temperature, chemicals, oxidative stress, heavy metals, ionizing and nonionizing radiation and ultrafine carbon black particles. Hsp70 has been shown to inteffere with postmitochondrial events to prevent free-radical-mediated apoptosis (Gotoh *et al.*, 2001). An increased expression level of Hsp70 can thus offer protection against stress. Heat-shock proteins are also involved in oncogenic processes (Jolly and Morimoto, 2000; Inoue *et al.*, 1999; French *et al.*, 2001). Some investigators have described increased heat-shock-protein levels after RF exposure (Leszczynski *et al.*, 2002; Kwee *et al.*, 2001; de Pomerai *et al.*, 2000). However, these results are controversial, because there are negative findings also (Cotgreave, 2005). It may be that data on Hsp70 awaits further confirmation, at different frequencies and power levels.

Nikolova *et al.* (2005) described modulation in gene regulation after RF-field exposure at an SAR of 1.5 W kg^{-1} in p53-deficient embryonic stem cells. Proteomic analyses of human endothelial cell lines showed RF fields induce changes in the expression and phosphorylation state of numerous proteins, including Hsp27.

Another important parameter is to measure neurotransmitters in various parts of the brain (Zhou *et al.*, 1986). Neurons transmit information across the synapses using a range of neurotransmitters. Calcium plays an essential role in this, because a small amount of calcium must enter the neuron every time before it can release its neurotransmitters. If the electromagnetic field causes extra calcium to leak inside the cell (neuron), it increases the background level and may trigger an early release of neurotransmitter. It has been shown that the excitation of acupuncture points by microwaves (0.2–3 GHz) may produce an efficient analgesic effect, as shown by

the corresponding increase in the pain threshold (Teng *et al.*, 1989). Furthermore, respective variations in pain threshold and neurotransmitter release in the center of pain reception in the brain are proportional (Van der Vorst *et al.*, 1992).

Particular interest has also been expressed in the biological effects of pulsed modulated RF and microwaves on the ear. The human ear can perceive pulsed modulated radiation between 200 MHz and 6.5 GHz as a buzzing or clicking noise, depending on the modulation characteristics. The effect is attributed to the thermoelastic expansion of the brain tissue, following the small ($\ll 1\,^{\circ}C$), but rapid, increase in temperature on the absorption of the incident energy, generating a sound wave in the head that is detected by the hair cells (cochlea) (Sienkiewicz *et al.*, 2005). However, its clinical potential is yet to be fully utilized.

106.10 MECHANISM OF ENERGY TRANSFER AND AMPLIFICATION

106.10.1 Macromolecular Resonance

Electromagnetic-field effects in biology and their variability are suggestive of the possibility of resonance effects. So far resonance conditions are characterized in terms of narrow 'windows', of frequency and amplitude ranges only (Blackman *et al.*, 1995).

There are two broad situations: when collisional perturbations are very short and when they are long in comparison with the field period. In the former case, every collision is quite effective in interrupting the molecule's radiation absorption–emission process. In a fluid with a high rate of collisions, a collisional broadened relaxation-type spectrum results. In the later case, whene collisions are of long duration compared to the EMF period, the spectrum becomes resonant. The collision time in a macromolecular fluid is a function of temperature, and therefore the EMF frequency determines the kind of spectrum (rotational or resonant). Water is a broad-band attenuator of microwave (MW) fields, which also shields other possible bimolecular absorption processes. Experiments suggest resonant absorption in growing cells at 41 GHz fields and in DNA at 11 GHz (Grundler *et al.*, 1977; Azanza and Del, 1994). However, the significance of these resonance frequencies in biological systems is yet to be established.

The nonthermal, pulsed microwave effects are connected with the transfer of information from the irradiating field to the live organism, through the latter's ability to identify certain frequencies of radiation, then its ability to absorb energy from the field (Hyland, 2001). The intensity of radiation needed for this recognition is many orders of magnitude below even that currently associated with nonthermal effects.

106.10.2 Stochastic Resonance

Fields millions of times weaker than the membrane potential gradient of $10^7\,V\,m^{-1}$ modulate cell processes to surface-stimulating molecules. This may underline the ability of biological systems to amplify small signals in noisy environments. Viewed in this manner; it is possible to imagine an information-processing system in which the presence of an ongoing noise-like activity enhances information-handling capacity. Low-level effects are attributed to the direct interaction between neuron membranes and the local electric fields. Power levels of 0.1 and 1 mW cm^{-2} correspond to free-space values of 61 and 194 V m^{-1}, respectively. This field is negligible compared to the static transmembrane potential of ~90 mV (~$10^7\,V\,m^{-1}$) across a membrane of thickness 4 nm. However, this is larger than the field due to slow brain waves (1 V m^{-1}) or from terrestrial fields (10^{-3}–$10^{-6}\,V\,m^{-1}$) (**Figure 6**).

106.10.3 Cell-Surface Glycoproteins as Possible Sites for EM-Field Interactions

Cells in tissue are separated by narrow fluid channels, typically not more than 150 A° wide, that act as windows on the electrochemical senses surrounding each cell. These channels are preferred pathways for intrinsic and environmental electromagnetic fields in tissue, since they offer a much lower electrical impedance than cell membranes. Functional measures of brain electrical impedance are thus an index of conductance in this extracellular space and have been correlated with brain tissue physiological states in health and disease (Adey *et al.*, 1963; 1965; Porter and Bocke, 1965). These intercellular channels are also the sites of electrochemical sensors that protrude as protein strands from within the cell membrane. They form a strongly negatively charged glycocalyx on the cell surface (**Figure 7**). They act as specific receptors for hormones, antibodies, neurotransmitter molecules, certain chemical cancer promoters and, maybe, EMF signals. Their amplified signals to the cell interior elicit enzymatic responses regulating metabolism, messenger functions and cell growth. McConnell (1975) noted that intrusion of the phospholipid tails are constrained and they behave more rigidly.

It is now established that cell Ca^{2+} signalling has extreme sensitivity for coherent excitation by field energies within specific amplitude and frequency windows (Schwartz *et al.*, 1990). Membranes are identified as sharply partitioning each cell from its neighbour, by reason of their high content of fat molecules (phospholipids). The structure is identified as double layer of phospholipid molecules, the plasma

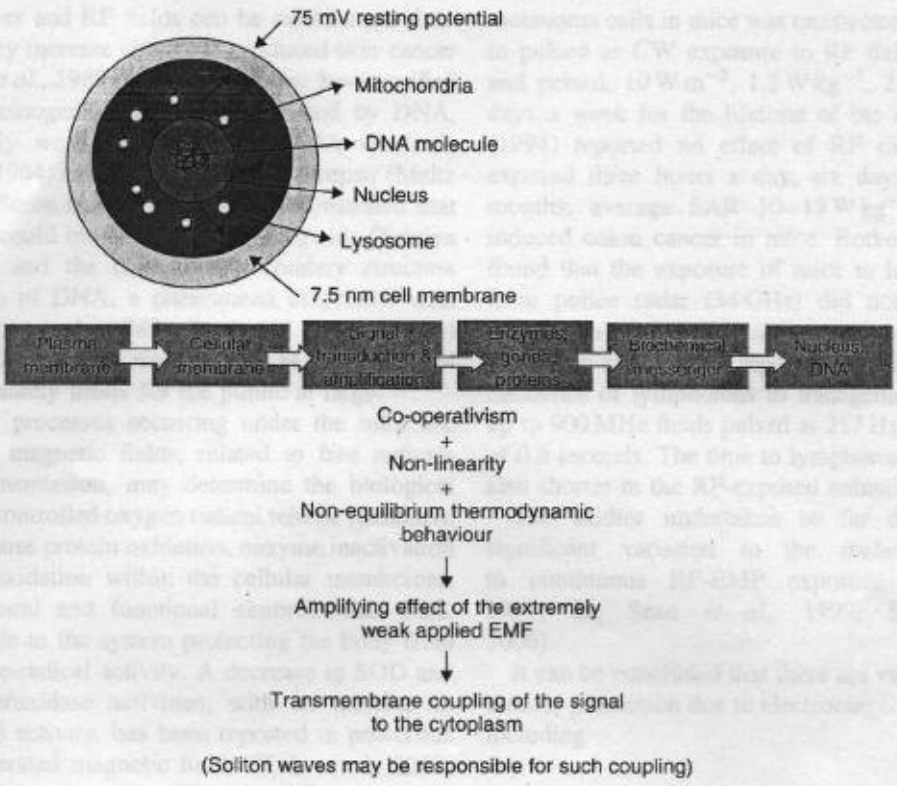

Figure 6 An idealized excitable cell at rest in the human body. 75 mV across a thickness of 7.5 nm corresponds to an electric field of 10 million $V m^{-1}$.

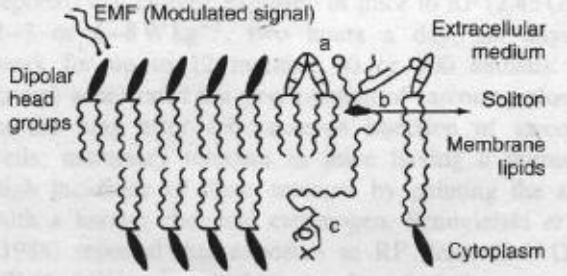

Figure 7 Model of the interaction between an EM field and the cellular system. a: glycocalyx; b: soliton; c: intracellular spacing. (Reproduced with permission from Lawrence and Adey, 1982. © Maney Publishing.)

membrane. The cell membrane is thus a physical and an electrical barrier. Since generally accepted physiological findings have revealed sensitivities to induced tissue electric gradients from ELF environmental fields and from ELF-modulated fields, it is anticipated that power amplification mechanisms are operative in transductive coupling of these weak stimuli from fluid surrounding cells to the cell interior.

In search for a general mechanism of interaction of EM field with cells, Na^+-K^+ ATPase, the 'ion-pump' enzyme in cell membranes has been studied (Behari *et al.*, 1998; Blank and Soo, 1992; 1991). Changes in enzyme activity in either electric or magnetic fields show that the most important factor affecting signal transduction is the level of enzyme activation, the maximum biological (ATP-splitting) activity of the enzyme under a given set of conditions (i.e. ion concentration, temperature). Enzyme function involves communication between ATP-splitting catalytic sites and ion-binding sites in different parts of the molecule in a coordinated sequence; ion-binding sites in enzymes are essential and are probably brought about by charge movements during function. Such movements have been observed in the microsecond range. Ion fluxes via effects on ion pumps such as Na^+K^+ ATPase in human red blood cells exposed to RF and microwave radiation (Allis and Sinha-Robinson, 1987; Liu *et al.*, 1990; Christiansen, 1989), pointed out dependence of the optical properties on membrane excitation. States may determine the stability of dark soliton propagation as a means of transmembrane signalling. This is summarized in **Figure 6**.

106.11 BIOMARKERS OF TUMOUR PROMOTION

From physical considerations it is suggestive that RF exposure is not mutagenic and is therefore unlikely to initiate cancers. Animal studies have demonstrated

that microwaves and RF fields can be called cocarcinogenic since they increase chemically induced skin cancer (Szmigielski *et al.*, 1982a). Cellular studies have verified that these carcinogenic effects are mediated by DNA, since relatively weak fields increase DNA synthesis (Liboff *et al.*, 1984) and can modulate DNA repair (Meltz *et al.*, 1987). Some studies have also demonstrated that electric fields could break or nick DNA strands (Tamiya *et al.*, 1988), and the change in secondary structure (conformation) of DNA, a phenomena associated with cancer (Kitchin *et al.*, 1989). It should be mentioned that these field emissions were largely at low EM field strengths, the safety limits for the public at large.

Intracellular processes occurring under the influence of power-line magnetic fields, related to free radicals and signal transmission, may determine the biological effects. An uncontrolled oxygen radical release (oxidative stress), may cause protein oxidation, enzyme inactivation and lipid peroxidation within the cellular membranes, causing structural and functional abnormalities. SOD plays a key role in the system protecting the body from destructive free-radical activity. A decrease in SOD and glutathione peroxidase activities, with an increase in catalase (CAT) activity, has been reported in powerline frequency-generated magnetic fields (Kula *et al.*, 2002) and in RF-field exposure alike (Kesari and Behari, 2008). It is possible that magnetic fields interact with the free radicals formed, rather than inducing them.

Szmigielski *et al.* (1982b) and Szudzinski *et al.* (1982) reported that chronic exposure of mice to RF (2.45 GHz, 2–3 or 6–8 $W kg^{-1}$, two hours a day, six days a week for up to 12 months; 40 or 100 animals per group) accelerated the development of sarcoma colonies in the lung after subcutaneous injection of sarcoma cells; mammary tumours in mice having a normally high incidence of these tumours by painting the skin with a known chemical carcinogen. Szmigielski *et al.* (1988) reported that exposure to RF fields (2.45 GHz CW, 4–5 $W kg^{-1}$, two hours a day, 5–6 days a week for a few months; 40 animals per group) increased the number of chemically induced hepatomas and sarcomas, and increased the number of skin tumours in mice given a subcarcinogenic dose of benzo[a]pyrene. The authors suggested that the acceleration of tumour development may have resulted from a direct effect on immunocompetent cells. However, no such effect was reported when exposed to a low-level microwave field after doses of 7,12-dimethylbenz[o]anthracene, a known carcinogen (Paulraj, 2000).

These results and other investigations are not without contradictions. Salford *et al.* (1993) reported no effect on the progression of tumour cells injected into rat brain after exposure to continuous or pulsed 915 MHz RF fields (CW exposure, 1 W per pulse, 1.67 $W kg^{-1}$, 0.41 $W kg^{-1}$ for 217 Hz modulation, pulse width 0.52 ms, 2 W per pulse, 62 animals per group). Santini *et al.* (1988) found that the progression of subcutaneously implanted melanoma cells in mice was unaffected by daily exposure to pulsed or CW exposure to RF fields (2.45 GHz CW and pulsed, 10 $W m^{-2}$, 1.2 $W kg^{-1}$, 2.5 hours a day, six days a week for the lifetime of the animal). Wu *et al.* (1994) reported no effect of RF exposure (2.45 GHz exposed three hours a day, six days a week for five months; average SAR 10–12 $W kg^{-1}$) on chemically induced colon cancer in mice. Rotkovska *et al.* (1993) found that the exposure of mice to low-level RF fields from police radar (34 GHz) did not affect biological parameters that could initiate any pathologic process. Repacholi *et al.* (1997) reported a 2.4-fold increase in the incidence of lymphomas in transgenic mice exposed to up to 900 MHz fields pulsed at 217 Hz with pulse widths of 0.6 seconds. The time to lymphoma development was also shorter in the RF-exposed animals.

The studies undertaken so far do not show any significant variation in the melatonin levels due to continuous RF-EMF exposure (Vollrath *et al.*, 1997; De Seze *et al.*, 1999; Sukhotina *et al.*, 2006).

It can be concluded that there are various indicators of tumour promotion due to electromagnetic-field exposure, including

1. Increase in ODC and PKC activity
2. Increase in Ca^{2+} efflux
3. Altered antioxidant enzyme activity
4. DNA strand breakage (single and double)
5. Na^{+}/K^{+} phosphatase activity
6. Decreased melatonin levels. ↓ Cancer promotion (Stress development/RF/MW syndrome)

It is quite intriguing that the mode of EMF interaction with biological system is multifold. There is ample evidence that low-level electromagnetic fields cause DNA strand breakage in brain cells and sperm. The application of pulsed electromagnetic fields to induced fracture and osteoporosis in rats causes accelerated healing (Behari, 1991) and deceleration in ovariectomized and neuroectomized rat (bones) (Lochan *et al.*, 2005; Jayanand *et al.*, 2003).

Some recent investigations (Prakash, 2008) have revealed that the synergistic effects of nanoparticles and pulsed electromagnetic radiation can prevent microgravity-induced osteoporosis. This is evidenced by an increase in bone mineral content, bone mineral density and morphological changes. Results indicate that the extremely low frequency field components of clinical pulsed elecromagnetic field (PEMF) signals are far more capable of stimulating bone remodelling activity than higher-frequency components. This is because the pulsed signals carry a multiplicity of messages to the biological systems compared to continuous ones. This in contrast to other low-level field effects, which are often implicated in tumour promotion. In contrast to high power, the use of weak electromagnetic fields to

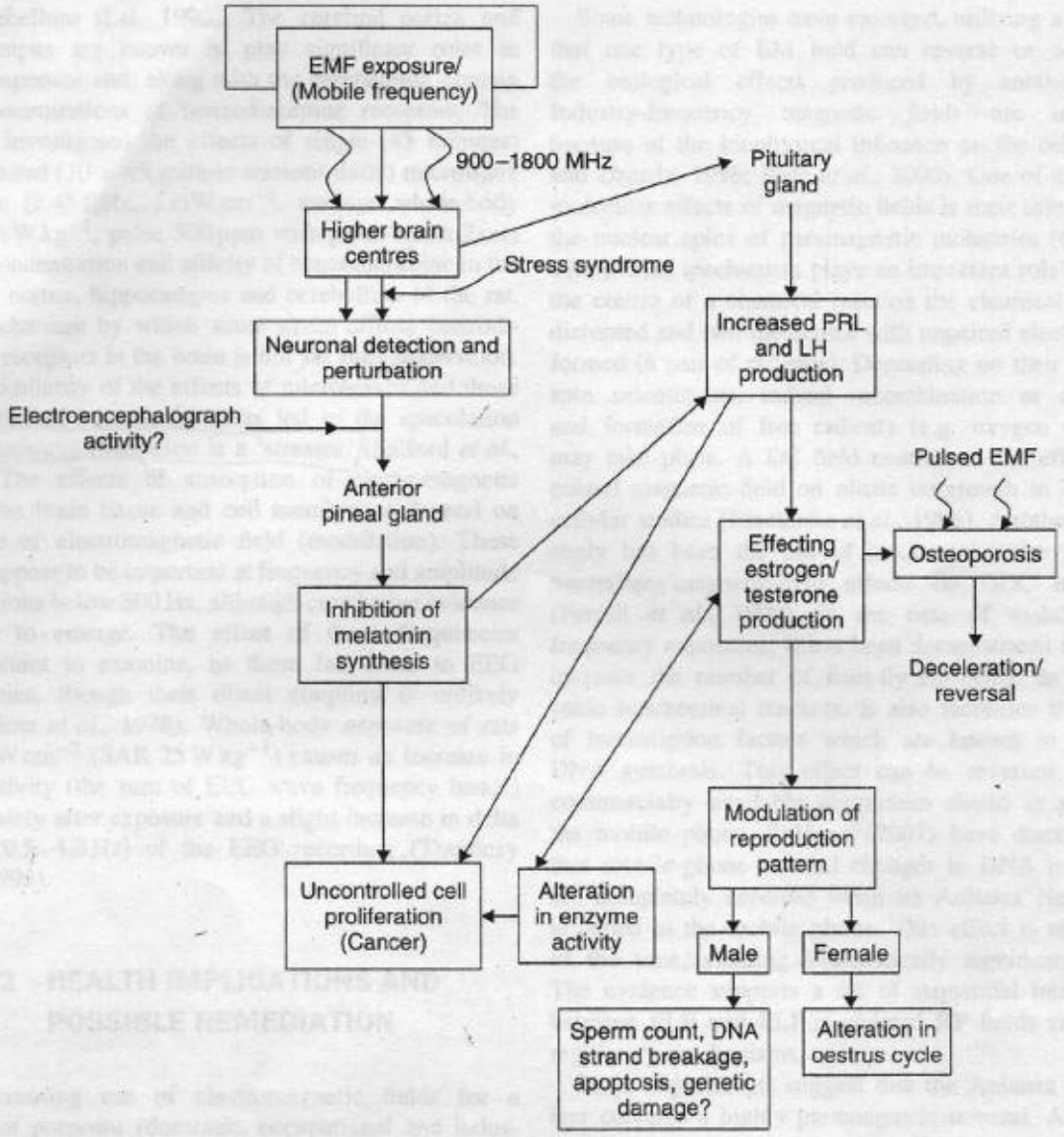

Figure 8 Proposed model of EMF exposure: influence on brain cells, promotion of the growth of initiated tumour cells, osteoporosis and reproduction patterns.

study the sequences and energetic events that couple humoral stimuli from surface receptor sites to the cell interior has identified cell membranes as a primary site of interaction with these low-frequency fields in pericellular fluid. A summary of the modes of EMF biointeraction is shown in **Figure 8**.

Long-term biological consequences of repeated microwave irradiation depend on the parameters of irradiation. Experiments have shown that changes in cholinergic receptors, after repeated microwave exposure, also depend on the endogenous signals in the brain. The microwave effects could be blocked by pretreatment, before each session of daily exposure, with the narcotic antagonist naltrexone. It is apparent from these results that endogenous opiods may play a mediating role in some of the neurological effects of microwaves (Lai, 1992). The microwave effects can be summarized as follows: (i) microwaves enhance morphine-induced catalepsy in the rat; (ii) narcotic antagonist blocks a transient increase in body temperature after microwave exposure; (iii) microwave-induced changes in high-affinity muscarinic cholinergic receptors in the brain after repeated sessions of microwave exposure can be blocked by pretreatment with a narcotic antagonist and (iv) the three major subtypes of opiod receptors, μ, δ and κ are involved in mediating the effect of microwaves in the brain.

The hypothesis that low-intensity pulsed microwave exposure can be a source of stress has been investigated by giving low intensity, single and repeated exposure to benzodiazepine receptors in three areas of brain: the cerebral cortex, the hippocampus and

the cerebellum (Lai, 1992). The cerebral cortex and hippocampus are known to play significant roles in stress responses and, along with the cerebellum, contain high concentrations of benzodiazepine receptors. The authors investigated the effects of single (45 minutes) and repeated (10 × 45 minute sessions daily) microwave exposure (2.45 GHz, 1 mW cm^{-2}, average whole-body SAR 0.6 W kg^{-1}, pulse 500 ppm with pulse-width 2 ms) on the concentration and affinity of benzodiazepine in the cerebral cortex, hippocampus and cerebellum of the rat. The mechanism by which acute stress affects benzodiazepine receptors in the brain is not yet fully understood.

The similarity of the effects of microwaves and those of established sources of stress led to the speculation that microwave irradiation is a 'stressor' (Salford *et al.*, 1994). The effects of absorption of electromagnetic energy on brain tissue and cell membranes depend on the type of electromagnetic field (modulation). These effects appear to be important at frequency and amplitude modulations below 300 Hz, although conclusive evidence has yet to emerge. The effect of these frequencies is important to examine, as these fall close to EEG frequencies, though their direct coupling is unlikely (Takashima *et al.*, 1978). Whole-body exposure of rats at 30 mW cm^{-2} (SAR 25 W kg^{-1}) causes an increase in EEG activity (the sum of EEG wave frequency bands) immediately after exposure and a slight increase in delta waves (0.5–4.0 Hz) of the EEG recording (Thuróczy *et al.*, 1994).

106.12 HEALTH IMPLICATIONS AND POSSIBLE REMEDIATION

The increasing use of electromagnetic fields for a variety of purposes (domestic, occupational and industrial) raises the problem of their health implications. Various functional properties of DNA (including DNA synthesis (Liboff *et al.*, 1984) and repair (Meltz *et al.*, 1987) are altered by EM fields. Direct effects on DNA may be mediated by its conformational state. Conformational states, in turn, are controlled by hydrogen bonds, which hold together the folded secondary structure of biomolecules (Takano *et al.*, 1999). Mobile phones speed up DNA rewinding, suggesting an increase in hydrogen-bond formation. If mobile phone radiation is found to have effect on hydrogen bonds, it will have serious implications in biology. This hypothesis, however, contradicts other data suggesting that the primary site of EMF biointeraction is the plasma membrane and/or the ions that bind to various protein receptors within the plasma, conditions requiring a complex interaction with the EM field from the mobile phone. In systems where two EM fields interact, the strength and orientation between the two fields is critical in order to obtain resonance conditions.

Some technologies have emerged, utilizing a concept that one type of EM field can reverse or neutralize the biological effects produced by another type. Industry-frequency magnetic fields are important because of the biophysical influence on the cell. (Kula and Drozdz, 1996; Kula *et al.*, 2000). One of the major molecular effects of magnetic fields is their influence on the nuclear spins of paramagnetic molecules (Grissom, 1995). This mechanism plays an important role when in the course of a chemical reaction the chemical bond is disrupted and two molecules with unpaired electrons are formed (a pair of radicals). Depending on their electron spin orientations, radical recombination or diffusion and formation of free radicals (e.g. oxygen radicals) may take place. A DC field neutralizes the effect of a pulsed magnetic field on nitrite outgrowth in neuronal cellular studies (Blackman *et al.*, 1996). Another related study has been the use of incoherent noise fields to neutralize magnetic-field effects on ODC induction (Farrell *et al.*, 1998). In the case of mobile-phone frequency exposures, it has been demonstrated that they increase the number of fruit-fly offspring, as well as some biochemical markers. It also increases the levels of transcription factors which are known to activate DNA synthesis. This effect can be reversed when a commercially available aluminium shield is added to the mobile phone. Syldona (2007) have demonstrated that mobile-phone-induced changes in DNA rewinding are completely reversed when an Aulterra Neutralizer is added to the mobile phone. This effect is seen 77% of the time, yielding a statistically significant result. The evidence supports a set of sequential interactions between ELF and ELF-modulated RF fields and some regulatory mechanisms.

Some experiments suggest that the Aulterra Neutralizer contains a highly paramagnetic mineral. A magnetoresistance response (Meissner effect) is induced when the neutralizer is in the presence of a magnetic field generated from mobile phones. Thus, paramagnetic shielding (in addition to ferromagnetic shielding) is probably the reason for the ability of the Neutralizer. RF exposure causing increased DNA damage in cells is cumulative. Various evidence suggests that responses of the central nervous system to this radiation could lead to a stress response (Lai, 1992; Lai *et al.*, 1987). Stress effects cumulate over time and involve first adoption and then an eventual breakdown of homeostatic processes when they persist. The results of major reports (WHO (World Health Organization), 2005; Seitz *et al.*, 2005; Rubin *et al.*, 2005) seem to support these findings.

In leukocytes, physiological activation is associated with the onset of phagocytosis and leads to increased formation of ROS. These cells exert a wide variety of functions including the regulation of the immune response (pro- and anti-inflammatory processes), scavenging of senescent cells, phagocytosis of infected or

malignant cells, wound healing, repair and detoxification. The generation of free radicals enhances important physiological processes, for example, signal-transduction processes of various membrane receptors and further immunological functions. An imbalance between excessive formation of ROS and the limited antioxidant defence system may take place. However, several authors (Lantow *et al.*, 2006a; 2006b; Simko *et al.*, 2006) reported no increase in free-radical level.

106.13 GUIDELINES FOR SAFETY LIMITS

The question of laying down the criteria for safe exposure is a problematic one, because the dose needs to be assessed, not just as external field intensity, but also as cumulative exposure, as well as SAR, for specific anatomical sites. This demands the need to have an accurate knowledge of RF exposure. This radiation is termed a silent killer; its impact is not immediately visible. Any epidemiological studies over a long period (10 years or more) are difficult to carry out and control. Moreover, the basic restrictions are expressed in quantities that are internal to the body and are not measured, such as SAR. On the other hand, the reference levels are expressed (measured) in the free-space situation, such as for the electric field. Such data are not always available.

Nonetheless, attempts to draw up safety limits and their criteria have long been in operation. RF exposure limits are defined by the ICNIRP (1998) and are set to $0.08\,W\,kg^{-1}$ for the general public and $0.4\,W\,kg^{-1}$ for occupational exposure. The guidelines for whole-body exposure on humans is based on responses to animals at levels sufficient to produce behavioural changes, but not thermal damage to the tissue. It is possible that, because of the large interspecies differences among the small animals (rodents) and primates, the former may not be representative of human responses under identical exposure conditions over the wholè body.

However, the latest basic restriction for localized exposure is $2\,W\,kg^{-1}$ for most parts of the body (Lin, 2006). For the extremities (arms and legs distal from the elbow and knees, respectively, including the fingers, toes, hands and feet) and for pinnae, the basic restriction expressed in terms of SAR is $4\,W\,kg^{-1}$. The value of SAR is obtained by averaging over some specified time periods (i.e. 6–30 minutes) and by averaging over any 10 g of tissue.

For frequencies between 3 and 100 GHz, the basic restrictions are the same as the derived limits of the MPE. The value of the MPE is obtained by averaging over some specified time periods that vary from 2.5 to 30 minutes for different frequencies.

The new Institute of Electrical and Electronics Engineers (IEEE) standard includes several major differences from the 1991 edition. First and the foremost, the IEEE standard instituted an exclusion for the pinnae or the external ears by relaxation of the abovementioned basic SAR restriction from 2 to $4\,W\,kg^{-1}$. Further, the SAR value has been raised from $1.6\,W\,kg^{-1}$ averaged over any 1 g of tissue, to $2\,W\,kg^{-1}$ over any 10 g of tissue. This effectively means relaxing the criteria, because deposition of energy over 10 g would be inherently lower, compared to the SAR over 1 g. This revised choice (10 g in the shape of a cube) would permit depositions of RF or microwave energy in different parts of the eye that exceed the basic SAR restriction by a large margin, while keeping the SAR for the entire eye below the prescribed limit ($2\,W\,kg^{-1}$).

In the 1991 edition, the MPE between 30 and 300 MHz, was $10\,W\,m^{-2}$. The new MPE in terms of power density is $2\,W\,m^{-2}$ between 30 and 400 MHz, the region most susceptible for human exposure. It ramps up from 2 to $10\,W\,m^{-2}$ between 400 and 2000 MHz. For frequencies greater than 2000 MHz, the MPE is $10\,W\,m^{-2}$. Also, the designated frequency bands and the MPE are different. In the 1991 edition, they were $10\,W\,m^{-2}$ between 30 and 300 MHz. The ramp up from 10 to $100\,W\,m^{-2}$ took place between 300 MHz and 3000 MHz. For frequencies greater than 3000 MHz, the MPE was $100\,W\,m^{-2}$ (**Figure 9**). In general, the new IEEE standards are more restrictive between 30 MHz and 100 GHz. Furthermore, new IEEE guidelines state that the maximum spatial power density should not exceed 20 times the square of the allowed spatially averaged peak values for frequencies below 400 MHz, and should not exceed $40\,W\,m^{-2}$.

The major differences also include the tissue mass and the time period over which the SAR values are to be averaged, and the applicable frequency bands for the MPE. Also, the most significant difference is the exclusion of pinnae from the head by IEEE, which made it possible to allow a higher local SAR value for the basic restriction at $4\,W\,kg^{-1}$. In the ICNIRP guidelines, pinnae are not excluded and are treated as an integral part of the human head.

Moreover, localized SAR values in the ICNRP guidelines are averaged over any 10 g mass of contiguous tissue. ICNIRP guidelines do not specify a cubic volume of tissue as the averaging mass. In addition, all SAR values are averaged over a six minute period in the ICNIRP guidelines, in contrast to the 2.5–30 minutes stipulated in the new IEEE standards.

The IEEE standards are not identical to the ICNIRP guidelines. This may also be true for frequencies used in mobile communications and wireless devices and systems. Global harmonization of RF exposure standards for the general public would be a future goal. Some of the points of contradiction, as mentioned above, will continue to be a point of investigation, and should also include more accurate assessment of SAR values,

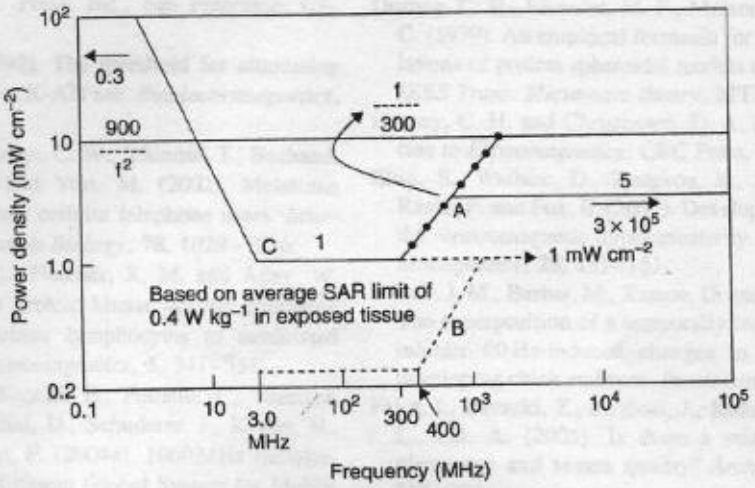

Figure 9 (A) New IEEE (2006) guidelines; (B) ANSI C 95.4 Subcommittee Human Exposure Guide (based on whole body exposure); (C) Old IEEE Guidelines.

more reliable (reproducible) biological results and an assessment of their impact on health.

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