Microthermal and Isothermal Biological Effects under Microwave Exposure

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I. INTRODUCTION

Rapid technological advances in electronics, electro-optics and computer science have set the stage for an unprecedented drive toward the improvement of existing medical devices and for the development of new ones. At the same time, safety concerns regarding the biological effects of electromagnetic radiation have been raised, including those at a low-level of exposure.

For many years, hyperthermia and the related radiometry has been a major subject of interest in investigating biological effects of microwaves. More recently, however, other subjects have received much attention, in particular: electromagnetic energy absorption in human subjects, especially in the human head and neck [1], interaction of microwaves with the nervous system [2], influence of the fields of mobilophony on membrane channels [3], and molecular effects [4].

An increasing amount of evidence, derived from *in vitro* and *in vivo* studies, indicates that microwave affect living systems directly. With microwave absorption, however, when experimenting with animals or humans, there are ambiguities concerning the relative contributions to physiological alterations of indirect thermal effects, microwave specific thermal effects, and possibly direct non-thermal interactions. Studies were conducted under conditions of precise and accurate temperature control, revealing direct effects at various frequencies and intensities on a number of cellular endpoints, including calcium binding, proliferation, ligand-receptor-mediated events, and alteration in membrane channels. Interactions occurring at the microscopic level are related to the dielectric properties of biomacromolecules and large molecular units such as enzyme complexes, cell-membrane receptors, or ion channels.

Excellent handbooks are available on the subject [4-6]. Specific European research was reviewed in 1993 [7]. There is now an abundant literature on the subject. A new book will soon be published, concentrating on applications and effects of radiofrequency and microwave fields, covering a frequency range from about 100 kHz to 10 GHz and above [8]. It is designed as a textbook: the reader will find problems at the end of each chapter. Starting with fundamentals in electromagnetics and biology, it extends up to applications, in particular medical.

Only the fields inside tissues and biological bodies can possibly interact with these: the biological effects of RF/Microwaves do not depend solely on the external power density; they depend on the dielectric field inside of the tissue or the body. Hence, the internal fields have to be determined for any meaningful and general quantification of biological data obtained experimentally. Dosimetric studies that attempt to quantify the interactions of radio frequency fields with biological tissues and bodies are reported.

Thermal considerations are of course an important subject. They are related to absorption. It is also important, however, to discuss the possibility of non-thermal effects, more specifically as micro-thermal effects - where microwaves act as a trigger - and isothermal effects - where thermodynamics are a necessary tool. In the latter case, entropy has to be considered simultaneously with energy.

II. SOME FUNDAMENTALS OF ELECTROMAGNETICS

The advances in RF/Microwave technology and computation techniques have paved the way for exciting new therapeutic and diagnostic methods. Frequencies, from radio frequencies (RF) as low as 400 kHz through microwave frequencies as high as 10 GHz, are presently being investigated for therapeutic applications in areas such as cardiology, urology, surgery, ophthalmology, cancer therapy and others, and for diagnostic applications in cancer detection, organ imaging, and more.

At the same time, safety concerns regarding the biological effects of electromagnetic radiation have been raised, in particular at a low level of exposure. A variety of waves and signals have to be considered, from pure or almost pure sine waves to digital signals like in digital radio, digital television, and digital mobile phone systems. The field has become rather sophisticated, and establishing safety recommendations or rules and making adequate measurements require quite an expertise.

At RF and microwaves, the electric and magnetic fields are simultaneously present: if there is an electric field, then there is a coupled magnetic field and *vice-versa*. If one is known, the other can be calculated: they are linked together by the well-known Maxwell's equations. It is interesting to be able to separate some biological effects due to one field from some due to the other field.

There is an interesting feature to note about microwaves: they cover, indeed, the frequency range where the wavelength is of the order of the size of objects of common use, *i.e.* meter, decimetre, centimetre, and millimetre, depending of course on the material in which it is measured. One may, hence, wonder whether such wavelengths can excite resonance in biological tissues and systems. We shall come back to this question.

Dielectric polarization is a rather complicated phenomenon [9]. The *dipolar polarization*, resulting from the alignment of

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the molecule dipolar moment due to an applied field, is a rather slow phenomenon. It is correctly described by a first-order equation, called after Debye [10]: the dipolar polarization reaches its saturation value only after some time, measured by a time constant called *relaxation time*□. The relative permittivity related to this phenomenon is a complex quantity, with real and imaginary parts. Dipolar polarization is dominant in the case of water, much present on earth and an essential element of living systems. The relative permittivity of water at 0°C is

$$\varepsilon_r = 5 + \frac{83}{1 + jf(GHz)/8.84(GHz)} \qquad (1)$$

The real part of the relative permittivity is usually called the *dielectric constant*, while the imaginary part is a measure of the dielectric losses. It can be shown that the imaginary part of permittivity is non-zero only when the real part varies as a function of frequency [11].

Generally, an effective conductivity is used when characterizing a lossy conductor, while the effective imaginary part of the permittivity is used when characterizing a lossy dielectric. At some frequency, the two terms are equal, in particular in biological media. Although both characterizations are equivalent, one needs to be careful when interpreting the results of an investigation.

Ionic polarization and *electronic polarization* are due to the displacement of the electronic orbits with respect to the protons when an electric field is applied. This phenomenon is much faster than dipolar polarization. It is a movement and is described adequately by a second-order equation, characterized by possible resonance [10].

When frequency increases, the electric and magnetic fields cannot be separated from each other: if one of the fields exists, so does the other. They are linked to each other in every situation, and this is described by Maxwell's equations. In living tissues, electromagnetic phenomena are usually slow, when compared to the extremely broad variety of phenomena to be evaluated. The shortest biological response time indeed is of the order of 10^{-4} second, while most of biological reactions are much slower. Hence, Maxwell's equations are most generally not used for evaluating biological effects in living tissues and systems: in practice, quasi-static approaches are quite satisfactory in biological material, and the electric and magnetic field are very often considered separately, even at RF/Microwaves.

Water is a dielectric material with a very high dielectric constant, of the order of 80 at low frequencies. Most of the living tissues contain a significant amount of water. As a consequence, the phase velocity at 1 GHz in a human body is almost 9 times smaller than in vacuum because the wavelength is almost 9 times smaller than in vacuum. At higher frequency, however, the permittivity decreases and the values of wavelength and phase velocity are closer to their values in vacuum.

Power absorption is a very important concept when investigating biological effects. It is also important when designing materials for protecting biological systems in an electromagnetic environment, including the medical environment. Recently indeed, electromagnetic environments have become very complex because of the wide and rapid spread of many kinds of electric or electronic devices, as exemplified by recent cellular telephone progress. As a result, electromagnetic wave interference problems due to these devices have increased in frequency.

The evaluation of biological effects, including *hazards*, and of medical applications is related to situations where biological tissues and living systems are placed in specific electromagnetic environments. Antennas transmit the fields. They may be placed for instance in free space and have other purposes than illuminating human beings, like transmitting television, FM-radio or mobile telephony signals. They may also be placed in specific locations, within a part of a human body, for instance, to exert a specific medical effect. In this case, the antennas are often called *applicators*.

The *reactive near field region* is the region immediately surrounding the antenna, and where the reactive field predominates. For most antennas, this region is commonly taken as interior to a distance $0.62(D^3/\lambda)^{1/2}$ from the antenna surface, where λ is the wavelength and D the largest dimension of the antenna. The region is called reactive because the reactive power density predominates in this region.

The *radiating near field* (Fresnel) *region* extends from the reactive near-field limit to a distance $2D^2/\lambda$ where D is the largest dimension of the antenna. For this expression to be valid, D must be large compared to the wavelength. It the antenna has a maximum overall dimension, which is very small compared to the wavelength, this field region may not exist.

The *far field* (Fraunhofer) region is commonly taken to exist at distances greater than $2D^2/\lambda$ from the antenna. This criterion is based on a maximum phase error of $\lambda/8$. In this region the fields are essentially transverse and the angular distribution is independent of the radial distance where the measurements are made.

When evaluating biological effects, it is very important to clearly distinguish between near-field and far-field exposure. The evaluation of hazards, due to RF/Microwave exposure on human beings or animals, is usually made in far-field conditions. Transmitting stations, indeed, are normally far enough from living and working situations on one hand, while the antenna of a mobile telephone is so small with respect to the wavelength that the head of an end-user is in the far field of the antenna. The evaluation of *specific biological effects* in medical applications is usually made in near-field conditions. When the antenna is used to deliver microwave power to heat tissue, the size and location of the microwave field have to be carefully located to control the affected tissue. Hence, the type and shape of the antenna are very much depending upon the specific application, and there are a variety of applicators. A main problem is of course that of matching the applicator to the tissue. On the other hand, electromagnetic energy transfer depends, to a great extent, on the absorption properties of the tissue. It also depends on the frequency. As an example, sources at millimetre waves yield results similar to infrared frequencies.

Some special care has to be exerted when the electromagnetic properties of a medium vary with frequency [11]. The medium is then said *dispersive*. It has been shown that such a material is necessarily *absorptive*. The fundamental problem is that, in this case, the electromagnetic energy has no precise thermodynamic definition. When the medium has limited dispersion, it is said *transparent*. This is the case when permittivity and permeability vary only slowly around the operating frequency.

Parameters of microwave exposure are an important consideration in the production of biological effects. One key word is *dosimetry*, which takes into account the level of exposure as well as its duration. The simplest expression is the product of the level by the duration. Different durations of acute exposure lead to different biological effects and, consequently, different long-term effects occur after repeated exposure. The waveform of the radiation is also important. Differential effects have indeed been observed after exposure to pulsed-wave with respect to continuous-wave microwaves. In practice, biological effects have been observed under a variety of exposure types: continuous wave (CW), sinusoidal amplitude-modulated wave (AMW), pulsed wave (PW), and pulsed modulated wave (PMW) [12].

Hence, there is a difficulty in evaluating the exposure. Thermal effects are of course related to power, so that comparison of biological effects under different types of exposure should be done at constant power. What is constant power, however? Normally it should be either the CW-power or the average power when the excitation is pulse modulated. In this case, however, and especially when the duty cycle is short, like in radar-type waves, the peak power may be much larger than the average power, and possible *non-linearity* may induce other effects. The difficulty should even be greater for microthermal or non-thermal effects, immediately influenced by fields and not by power. This is a controversial question. We should not consider power, however, as the only parameter able to induce effects. For instance, differential effects have also been observed after exposure to plane- *vs.* circular-polarized waves.

III. PENETRATION IN BIOLOGICAL TISSUES AND SKIN EFFECT

Biological materials are not good conductors. They do conduct a current, however, because the losses can be significant: they cannot be considered as lossless. Solving the diffusion equation, which is valid mainly for good conductors, where the conduction current is large with respect to the displacement current, shows that the amplitude of the fields decays exponentially inside of the material, with as decay parameter

$$\delta = 1/(\omega\mu\sigma/2)^{1/2} \qquad \text{m} \qquad (2)$$

The parameter δ is called the *skin-depth*. It is equal to the distance within the material at which the fields reduce to 1/2.7 (approximately 37%) of the value they have at the interface. One main remark is that the skin-depth decreases when the frequency increases, being inversely proportional to the square root of frequency. It also decreases when the conductivity increases: the skin-depth is smaller in a good conductor that in another material. For most biological materials the displacement current is of the order of the conduction current over a wide frequency range. When this is the case, a more general expression should then be used instead of (2) [13]. The skin depth is equal to 1.5 cm at 900 MHz and is of the order of one millimetre at 100 GHz in living tissues.

Shielding is much easier to achieve at high frequencies than at low frequencies. Skin effect implies that the higher the frequency the smaller the penetration, which may lower the efficiency of a medical application. Hence, the choice of frequency is important. On the other hand, it also implies that if a human being, for instance, is submitted to a microwave field, its internal organs are more protected at higher than at lower frequencies. As an example, the skin-depth is 3 times smaller at 900 MHz, a mobile telephony frequency, than at 100 MHz, an FM-radio frequency, which means that the fields are 3 times more concentrated near the surface of the body at 900 MHz than at 100 MHz. It also means that internal organs of the body are submitted to higher fields at lower than at higher frequency.

Table 1 summarizes some skin depth values for human tissues at some frequencies. The electromagnetic properties of the tissues as well as their variation as a function of frequency have been taken into account.

In the general public, there is a tendency to believe that RF and microwaves exert more significant biological effects than low and extremely low frequencies. This is not necessarily true: the dielectric constant of living materials is about 10,000 (ten thousand) times larger at extremely low frequency (ELF) than at microwaves. The dielectric constant is important, because it is the link between the source field and the electric flux density (also called displacement field). A dielectric constant 10,000 larger implies the possibility of an electric flux density of a given value with a source field 10,000 times smaller. Figure 1.shows the dielectric constant of living material (muscle) as a function of frequency. There is a level of about 1,000,000 at ELF, up to 100 Hz, then a second level of about 100,000 from 100 Hz to 10 kHz, and, after some slow decrease, a third level of about 70-80, from 100 MHz to some GHz. This last value is that of the dielectric constant of water at microwaves. One of the main constituents of human tissues is water. Hence, human beings have about the same microwave properties as water.

TABLE I
TYPICAL SKIN DEPTHS IN HUMAN TISSUE

	Radio FM	**TV Transmitter**	**GSM Mobile**	**DCS Mobile**
Frequency (MHz)	100	450	900	1 800
Skin depth (cm)	3	1.5	1	0.7
Depth at which power reduces to 1% (cm)	9	4.5	3	2

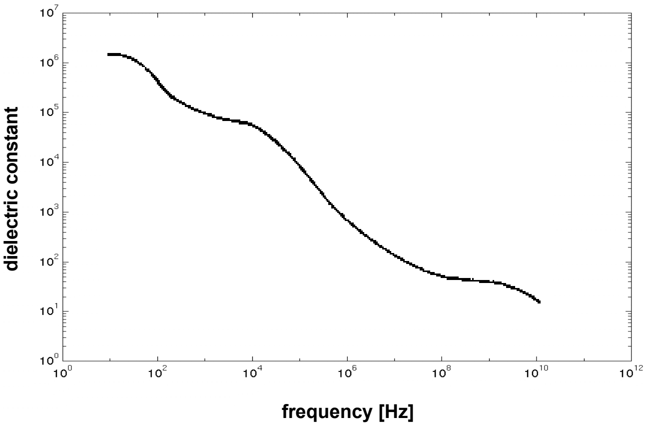

Figure 1. Dielectric constant of living material as function of frequency

A good knowledge of the complex permittivity of biological media is necessary for evaluating biological effects as well as in medical applications. A number of measured data are available for characterizing biological media. It should be mentioned, however, that there are not many measured data for biological and organic liquids at frequencies above 20 GHz.

The dielectric constant is the real part of the complex relative permittivity. It is of primary importance when characterizing dielectrics. It should not be forgotten, however, that the permittivity is complex in the frequency domain and that the dielectric constant gives only partial information. Up to about 1 GHz, materials respond to *relaxation* phenomena. The process is rather complicated. The task of dielectric theory is difficult not so much because permanent dipoles cannot always be identified, but mainly because they influence mutually one another: a dipole is not only subject to the influence of a field but also has a field of its own. The mutuality of the influence of dipoles, permanent or otherwise, on one another makes the response of the assembly a cooperative phenomenon, depending on the size and shape of the assembly [10].

The relaxation process consists in the approach to equilibrium of a system, which is initially out of thermodynamic equilibrium. Such a process is *irreversible*, and not covered by equilibrium thermodynamics. Most relaxation processes fulfill the conditions for which irreversible thermodynamics is applicable. Relaxation occurs when the free energy stored in the system is degraded into heat, in other words: if entropy is created irreversibly. The irreversibility is related to the fact that the free energy of the field is used to increase the total amount of heat stored in the dielectric plus the heat reservoir surrounding it. The thermodynamic treatment illuminates the significance of some of the concepts of relaxation, and shows, in particular, that the Debye equation is the most plausible description of a relaxation process in first approximation.

Relaxation refers to that part of polarization that is due to the ordering of permanent dipoles. However, matter can take up energy out of a field even in the absence of permanent dipoles if the field perturbs oscillations of one kind or another. The polarization caused by this mechanism is called *electronic polarization* or *optical polarization*.

IV. SOME FUNDAMENTALS IN BIOLOGY

The effects of the interaction of radio frequency and microwave radiation with biological tissues can be considered as the result of three phenomena:

1. The penetration of the electromagnetic waves into the living system and their propagation into it.
2. The primary interaction of the waves with biological tissues.
3. The possible secondary effects induced by the primary interaction.

The word *interaction* is important. It stresses the fact that end results depend not only on the action of the field but are influenced by the reaction of the living system. Living systems have a large capacity for compensating for the effects induced by external influences, in particular electromagnetic sources. This is very often overlooked while it is one main reason for which conclusions derived from models have to be taken with precaution. *Physiological compensation* means that the strain imposed by external factors is fully compensated and the organism is able to perform normally. *Pathological compensation* means that the imposed strain leads to the appearance of disturbances within the functions of the organism and even structural alterations may result. The borderline between these two types of compensation is obviously not always easy to determine.

Bioelectricity is extremely important in a living body. It has been shown since quite a time that direct application of an externally generated voltage may have an effect on bone and cartilage repair. Considerable animal and *in vitro* experimentation suggests the clinical usefulness of electric currents for soft tissue repair, and possibly to enhance repair of nerve fibres that have sustained crush or transsection injury [14]. There is no doubt that bioelectricity has to be taken into account seriously when investigating possible medical applications of radio frequencies and microwaves, as well as when wondering about possible hazards on human beings and animals due to radio frequencies or microwave exposure.

The above description of dielectric properties of materials was limited to bulk homogeneous materials. The dielectric properties of tissues are to be investigated into more detail, in particular for heterogeneous materials. Three relaxation processes are mainly responsible for the dielectric properties of tissues: dipolar orientation, interfacial polarization, and ionic diffusion. The usual theories apply to linear responses to weak fields. As the field intensity is increased, at some level the response will no longer be linear. The threshold at which non-linearity becomes noticeable depends on the system and of the investigated dielectric effect. Non-linearity thresholds have been evaluated [15].

When a material has parameters like permittivity, conductivity, and/or permeability varying as a function of frequency, it is said dispersive; this property is called *dispersion*. On the other hand, when a material has a non-zero imaginary part of the permittivity (or of the permeability), it exhibits losses and is said *dissipative* (or *lossy*); this property is called *dissipation*. It can easily be proven that dissipation induces dispersion and reciprocally, in a universe satisfying causality, however.

It has already been said that water is the major constituent in most tissues. The water contained in tissues is sometimes called *biological water*. It is obviously difficult to evaluate the differences between bulk tissue water and bulk water. Dielectric relaxation, conductivity, and diffusion have been investigated for the sake of comparison. For instance, Cole-Cole representations show a relaxation time of the water in muscle tissue 1.5 times longer than that of pure liquid water, which is not much of a difference [15].

The astonishingly high value of the permittivity at ELF (Fig. 1), due to the *alpha* dispersion, can be largely ascribed to *counterion* diffusion effects. Theory predicts a dielectric increment of the order of 10^6 [16-17]. The alpha-dispersion also results from other contributions: active membrane conductance phenomena, charging of intracellular membrane-bound organelles that connect with the outer cell membrane, and perhaps frequency dependence in the membrane impedance itself [18]. Although the alpha dispersion is very striking in the permittivity, it does not appear in the conductivity. Assuming a dielectric increment of 10^6 and a relaxation frequency of 100 Hz, the Kramer and Kronig's relations yield a total increase in conductivity associated with the alpha-dispersion of about 0.005 S m^{-1} while the ionic conductivity is about 200 times larger. Thus, at low frequencies, tissues are essentially resistive despite their tremendous permittivity values.

The *beta*-dispersion occurs at radiofrequencies. It arises principally from the capacitive charging of cellular membranes in tissues. A small contribution might also come from dipolar orientation of tissue proteins at high radiofrequencies. As an example, blood exhibits a total dielectric increment of 2,000 and a beta relaxation frequency of 3 MHz [15]. The associated increase ion conductivity is about 0.4 S m^{-1}. For tissues, the static permittivity and relaxation times of this dispersion are typically larger than in blood.

The *gamma*-dispersion occurs with a centre frequency near 25 GHz at body temperature. It is due to the dipolar relaxation of the water that accounts for 80% of the volume of most soft tissues, yielding a total dielectric increment of 50. These values of dielectric increment and relaxation frequency yield a total increase in conductivity of about 70 S m^{-1} [15].

Some authors have called *delta*-dispersion a small dispersion occurring in tissues and other biological materials between 0.1 and 3 GHz. The lack of a single dominant mechanism makes the interpretation of this dispersion region difficult.

The low-frequency conductivity of *muscle tissues* has been reviewed in detail. Muscle exhibits an extreme anisotropy in its configuration and hence in its electrical properties: there is a seven- to ten-fold variation in conductivity and permittivity (of dog skeletal muscle) at low frequencies. Similar variations have been reported in skeletal and heart muscle from many other species. For muscle tissue oriented perpendicular to the external field, the plateau between the alpha- and the beta-dispersion is at about 10^5 and the relaxation frequency is around 250 kHz. In the longitudinal orientation, the conductivity at low frequencies is higher and varies much less as a function of frequency. At microwaves, there is not really a distinct separation between the beta- and higher-frequency dispersions.

There has been interest on other *soft tissues* with high water content, like liver or breast tissue, either normal or tumoral. The main non-water component of soft tissue is *protein*. At radiofrequencies, beta-dispersion is related to a broad distribution of relaxation times, which arises principally from the presence of membrane-bound structures of widely varying dimensions. A simple model for liver, assuming that the contributions to the permittivity from each major tissue structure are additive, yields remarkably good agreement with the measured properties of the tissue above 1 MHz [19]. One main result is that the dielectric dispersion in liver tissue in the range of 1 to 100 MHz represents the high-frequency end of the beta-dispersion of the cells together with the organelles.

Tumour tissues have often been found noticeably different from normal tissues, but not in all the experimental data [15]. They have significantly higher water content than normal tissues. Necrosis in the tumour leads to breakdown of cell membranes, so that a larger fraction of the tissue can carry current at low frequencies. Experimental data showed that necrosis yields a five- to ten-fold higher conductivity while the permittivity is generally smaller than that of normal tissue. The infiltration in normal tissue of neoplastic tissues of high water content leads to pronounced changes in the dielectric properties, for instance in breast tissues. The practical significance of these differences however is unclear.

The dielectric properties of *bone* have also been investigated under near-normal physiological conditions. The conductivity of bone at low frequencies is associated with fluid-filled channels that permeate the tissue, and is proportional to the conductivity of the medium surrounding the tissue. The DC-conductivity varies by a factor of three with orientation. The corresponding variation of permittivity is largely unknown. Fluid-saturated bones exhibit a permittivity of about 1,000 at audio frequencies, decreasing to 10 to 20 at 100 MHz. The conductivity increases by about 0.05 S m^{-1} over the same frequency range. This dispersion can be fitted by a Cole-Cole function with distribution parameter □ = 0.5 and a centre relaxation frequency of a few kHz [20-21].

Adipose tissues like fat and bone marrow are distinguished by their low water content and by cells largely filled with lipids. Fat and bone marrow show a large alpha-dispersion between 10^4 and 10^5 Hz. The beta-dispersion is either absent or small in comparison with that of soft tissues. It has been observed that the conductivity of fat samples is higher than that of a soft tissue like liver, probably because of its larger extracellular fluid fraction [22].

Information about the influence of *temperature* on the electric parameters of the material may be needed for some applications. At low frequencies, below the beta-dispersion, the conductivity reflects the volume fraction of extracellular space. For small temperature increases, it has been reported that the conductivity properties of tumour and normal tissue, at 44 kHz and at 1 MHz, varied reversibly, with a temperature coefficient of about 2% per degree C. These changes reflect thermally induced changes in the conductivity of tissue electrolyte. For large temperature increases (above about 44.5°C), however, the dielectric properties exhibit abrupt and irreversible changes, reflecting *thermal damage* to the tissue. In excised tissue maintained at 44°C, the low-frequency conductivity decreased initially by approximately 10% during the first hour, then gradually increased by approximately 50% during the next 8 hours; tenfold changes were reported in the permittivity over similar periods [15]. Hence, monitoring temperature is accompanied with a lot of uncertainty.

V. THERMODYNAMICS

Electromagnetic properties are only one way to characterize materials. Poynting's theorem expresses equality between the space variation of the electromagnetic power and the time variation of the electromagnetic energy. It is well known that electromagnetic theory is connected with the structure of the problem, in particular with boundary conditions. It must be noticed, however, that *temperature is not an electromagnetic parameter*: it is a consequence of energy absorption at RF and microwave frequencies. The *specific absorption rate* (SAR, W/kg) is proportional to absorption losses, and there is a temperature elevation when SAR is positive: if there is absorption, there is a temperature elevation. Hence, from a phenomenological point of view, it should be emphasized that electromagnetic theory does not possess the mathematical tool for imposing a constant temperature. As a consequence, it cannot investigate the possibility of non-thermal effects: when using electromagnetic theory, only thermal effects can be evaluated. In other words, *using exclusively electromagnetic tools offers no chance to display non-thermal effects*. If electromagnetic energy is not an adequate tool for investigating non-thermal RF and microwave effects, then what is the good tool? Obviously, other considerations have to be taken into account, in which temperature is a parameter. This of course leads to thermodynamics.

Contrary to electromagnetic theory, thermodynamics has no connection with the structure of the system. It considers the system as a "black box", with four parameters: volume, pressure, temperature, and entropy. Hence, thermodynamics is able to investigate effects at constant volume, or constant pressure, or also constant temperature. In other words, to investigate the possibility of *isothermal* effects, electromagnetics and thermodynamics have to be used jointly, combining Poynting's theorem with basic thermodynamic equations. Hence, one has to investigate to what extent energy and entropy can be used in combination to evaluate isothermal effects. This of course seriously complicates the study.

Originally, thermodynamics had to do with the conversion of heat into work. The efficiency, ratio of the useful mechanical work to the used heat, became the principal characteristic of this conversion. In 1854, Clausius introduced the new concept of *entropy* [23], defined by

$$S = dQ / T \tag{3}$$

where S is the entropy, Q is the heat and T is the temperature in K. He formulated the second law of thermodynamics as

$$dS \geq 0 \tag{4}$$

where equality is applicable for reversible processes and inequality for irreversible processes. In 1877, Boltzmann published the statistical character of the second law of thermodynamics by determining the relation between the entropy and the probability of the system state. In 1947, Prigogine showed that the entropy of a system could be split in two parts [24]:

1. The flow of entropy due to interactions with the environment.
2. The entropy generation inside the system.

The second part is characteristic of the thermodynamics of *irreversible processes*.

A simple medium, like a lossless dielectric medium, exhibits no dispersion, *i.e.* its electrical characteristics do not vary with frequency. In this case, the electromagnetic energy has an exact thermodynamic significance: it is the difference between the internal energy per unit volume with and without the field, respectively, with unchanged density and entropy. In the presence of dispersion, however, no such simple interpretation is possible. Moreover, in the general case of arbitrary dispersion, the electromagnetic energy cannot be rationally defined as a thermodynamic quantity [25]. This is because the presence of dispersion in general signifies a dissipation of energy, which is the reason why a dispersive medium is also an absorbing medium.

These considerations have then been generalized [26]. Any thermodynamic system may be described by a total energy U, sometimes termed the *internal energy*. Since it is not really possible to define absolute zero-energy conditions, energy is generally measured with respect to some arbitrary reference conditions, for instance zero-temperature. It is, however, possible to define, precisely, *changes* in energy. For example, if a change in volume dV of a system occurs while a given pressure is applied, the change in internal energy will be $dU = -pdV$. Other sources of energy are electric fields, magnetic fields, stresses, and sources of heat energy. Each means of altering the system energy involves some external force function whose magnitude is independent of the size of the system: electric field $\overline{E}$, magnetic field $\overline{H}$, stress $\overline{T}$, and temperature T. These variables are termed *intensive variables*. The changes in the system are proportional to the number of particles in the system; they are termed *extensive variables*: volume V, electric polarization $\overline{P}$, magnetic polarization $\overline{M}$, and strain $\overline{S}$. A differential change of system energy may be expressed as a function of these quantities and of dQ, *heat input* to the system.

When there is heat input to a system maintained at thermal equilibrium, the differential dQ equals TdS, where T is the temperature and S the entropy, a complementary extensive variable. Suppose that a system is composed of two parts, A and B, each of which is at thermal equilibrium but having different temperatures T_A and T_B, respectively. If a quantity of heat energy dQ passes out of part A into part B, the change of entropy of part A must be $-dQ/T_A$ $(= dS_A)$. The change of entropy of part B is dQ/T_B $(= dS_B)$. The change in entropy of the entire system is $dQ(1/T_A - 1/T_B)$. The heat will flow from the hotter part to the colder part; hence, if $T_A > T_B$, the system will experience a net *increase* in entropy *without* the addition of heat energy from an external source. The entropy of the overall system will continue to increase until the temperatures of the two parts become equal. This type of change is termed an irreversible change, for there is nothing one can do to the entire system from outside to re-establish the temperature difference that existed initially.

VI. NON-THERMAL, MICROTHERMAL, AND ISOTHERMAL EFFECTS

For humans exposed to very low power densities (between a few □W cm^{-2} and a few mW cm^{-2}), East European epidemiological studies [27-29] have revealed a variety of reversible asthenic problems that constitute the hypothetical *microwave syndrome* (headache, perspiration, emotional instability, irritability, tiredness, somnolence, sexual problems, loss of memory, concentration and decision difficulties, insomnia, and depressive hypochondriac tendencies). There was, however, no control group. Furthermore, the evaluation of these complaints is difficult in the absence of well-established dosimetric data. Individuals suffering indeed from a variety of chronic diseases may exhibit the same dysfunction of the central nervous and cardiovascular systems. Hence, it is extremely difficult, if not impossible, to rule out other factors in attempting to relate microwave exposure to clinical conditions. These problems may well be due to environmental factors unrelated to microwaves, but a possible non-thermal mechanism cannot be completely ruled out [30]. On the other hand, the controversy regarding whether radiofrequency radiation sickness is a medical entity has recently been revisited [31]. In Western Europe, there are now a number of persons complaining about suffering from a variety of effects caused, as they say, by the GSM signals.

The possibility of either non-thermal or micro-thermal effects is not a recent question. One needs to be very careful about the conditions of an experimental study when investigating the possibility of non-thermal effects, to be sure to take into account all the power components. It is obviously indispensable to be able to distinguish between thermal and non-thermal effects.

There is quite a controversy about the possibility of non-thermal or microthermal effects. This controversy is not only scientific: it is largely political and commercial. Accepting indeed the idea that RF or microwave exposure may cause non-thermal effects implies that such an exposure could be of a low or very low level, and this is not well accepted. On the other hand, it is a rather common mistake to consider that biological effects are almost necessarily pathogenic for human beings. This is not true: biological effects may or may not result in an adverse health effect. As a matter of fact, this is the whole question about how to establish guidelines for limiting EMF exposure: they must provide protection against known adverse health effects. Accepting or rejecting non-thermal effects is not a minor question. In 1971 already, Michelson and Dodge, comparing Soviet and Western views on the biological effects of microwaves, mentioned: "The importance of the difference between the Soviet and Western views is readily apparent when it is realized that practical consideration of Maximum Permissible Exposure (MPE) is based on the acceptance or rejection of non-thermal effects of microwaves as biologically significant" [32].

On the other hand, investigating the possibility of isothermal effects does not preclude the attention to be paid to "non-thermal" effects, which should probably better be termed *microthermal* effects [33]. The question is: can extremely weak electromagnetic exposure have large biological effects, and how is this possible? One then has to consider the possibility of *trigger action* by microwaves.

It is tempting to link frequency-dependent biological effects of resonance type to absorption bands in certain biomolecules. Fröhlich has demonstrated, however, that such resonances are properties of the *whole system*, and may depend on the biological activity. Biological systems have to be considered in terms of their activities, which require a high degree of organization. Such organization may be of a complex nature, but it does require consideration of the system as a whole [34]. It is important to realize that in some instances biosystems can exhibit properties similar to those of the most refined electronic instruments, achieving this with the use of biomolecules in a way that is not well understood. For instance, at low intensities, the human visual system has a *sensitivity* that is close to the theoretical limit. Comparing the energy of a light quantum with that of a nerve impulse shows that there is a gain of more than 10^6. Clearly the light quantum acts as a trigger for a nerve impulse, the energy of which is provided by the biological system.

Control of activities represents another important set of *in vivo* biological properties. It must be well understood that for instance the absence of control of cell division consists in cancer. Of particular interest among materials are enzymes, which through their catalytic action regulate most biological chemical processes. Of particular interest also is of course the maintenance of the electric potential difference across biological membranes, with a thickness of about 10 nm.

Macroscopic organization is, of course, uniquely correlated to details of microscopic structure. This does not mean, however, that knowing all microscopic details will reveal the interesting macroscopic properties. The number of microstates is indeed so enormous that it cannot be handled. Furthermore, the relevant macroscopic properties are expressed in terms of concepts that do not exist in microphysics: they are collective properties. In these circumstances, the use of the concept of *information*, which is negative entropy, cannot be useful. For instance, the enormous number of microstates may lead to a corresponding information content of the order of 200 log 20.

It is a general feature of active biological systems that energy is always available, through metabolic processes, and that this causes non-linear changes in molecules, or large subsystems. Hence, from the point of view of physics, there are non-linear effects that change with time and are maintained through constant energy supply. It is dangerous, therefore, to extrapolate from properties of biological molecules, obtained by extracting them from the living system, to their behaviour *in vivo*, although in some cases this can be done. Still, biological systems are relatively stable from a microscopic point of view: the thermal vibrations of single atoms are practically the same as in a corresponding non-biological system. In some respect, however, involving relatively few degrees of freedom, they are very far from the thermal equilibrium, and these degrees of freedom dominate the overall behaviour of the rest. They may be described in terms of collective properties or organizations that do not exist in individual particle physics. These collective properties evolve as a consequence of supply of energy (metabolism), and usually represent extreme non-linear displacements.

Two theoretical physical models have been presented in detail [34]. An essential feature in both cases is the basic importance of the *non-linear characteristics* in conjunction with a supply of energy. One model is quasi-static, showing that under very general conditions metastable states with very high electric polarization exist. The second is dynamic in terms of *coherent excitation of electric vibrations*. It shows that under more stringent conditions coherent electric vibrations may be excited by random metabolic energy. This leads to long-range selective forces that supplement short-range forces, including those leading to standard chemical processes. The selectivity of the long-range forces depends on the frequency of the oscillating systems, which in turn depends on their structure.

Biological membranes have been considered as a basic material, showing oscillations with displacement perpendicular to the surface, so that for the longest wavelength the membrane thickness equals half the wavelength. Assuming elastic properties corresponding to an acoustic velocity of 10^3 m s^{-1} yields a frequency 0.5×10^{11} Hz, *i.e.* the microwave frequency 50 GHz. The membrane is not homogeneous, however, because a considerable number of proteins are dissolved in it, so that small sections of the membrane may of course vibrate separately from the rest. The membrane is very strongly polarized electrically, with a field of about 10^7 V m^{-1}. Hence excitation of vibration of a particular section of the membrane is connected with a vibrating electric dipole. Multipoles may lead to higher frequencies. Of course, molecules outside the membranes may also oscillate as well as other sections of a cell. There may also be other sources of oscillations, like plasma modes of the unattached electrons for instance. As a consequence, a great variety of possible frequencies will exist.

Quite logically now, the question is: what is the possibility of trigger action by microwaves? Fröhlich pointed out theoretically the possibility of coherent excitations, showing that when certain conditions are fulfilled, random energy supply to the modes of a band of electric polarization waves may lead to strong, *i.e.* coherent, excitation of a single mode provided the energy supply exceeds a critical value. Trigger action of microwaves is one feature of the model. The other is that it predicts strong excitation of polar modes through biological pumping.

Non-thermal action of microwaves can be evoked at this stage. Microwaves penetrating into a material deliver energy to it, as a linear response proportional to the intensity of the radiation and with a magnitude and phase dependence governed by the complex permittivity of the material. There is an action of microwaves on the thermal motion of the electric dipoles of the material. This motion is only very minutely perturbed but this induces an increase in temperature: under stationary conditions, the energy removed by heat conduction is equal to the energy supplied by the absorption of the microwaves. Consequently one should not expect too much the detection of non-thermal effects in regions of high dielectric absorption.

There is also one general argument in favour of such a mechanism. One of the most general biological features is indeed that energy supplied in terms of food, or of sunlight, is in part used to build up and maintain a very complex organization. The sun may well warm a plant. Nobody says, however, that the action of the sunlight on a plant is exclusively thermal.

The concept of *entropy* has been shown to be necessary to evaluate correctly some phenomena in electronics engineering. One typical example from literature is *luminescence*, with the problem of conversion of heat into luminescence radiation. The heat comes from the thermal energy of the crystal lattice. It has been shown that the ratio between the luminescence energy and the absorbed excitation radiation energy - the energy efficiency - can be larger than unity, at the expense of the thermal energy of the lattice [35]. This results in the *cooling* of the lattice, often termed optical cooling. The phenomenon can be explained by analogy with a heat engine. When a motor transforms heat into mechanical work, less-ordered energy is transformed into more-ordered one, and the efficiency is limited by thermodynamic considerations. On the other hand, when the motor transforms mechanical work into heat, more-ordered energy is transformed into less-ordered one, and the limit efficiencies are larger than one. Hence, limit efficiency larger than unity for luminescence implies a process in which the emitted radiation is less ordered than the energy being transformed.

Luminescence is a process in which electromagnetic radiation interacts with matter, producing a direct conversion of radiant energy into electrical energy. Luminescent systems are closed systems, in the thermodynamic sense of the word: they can exchange energy with the environment. Another example is a photochemical system: such systems can be open systems, able to exchange both energy and mass with the environment.

The ratio of the useful electrical work to the absorbed part of the electromagnetic radiation energy is termed the *efficiency* of the converter. On the other hand, the ratio of the useful electrical work to the total electromagnetic radiation energy is termed the *effectiveness*. The effectiveness is equal to the efficiency when the electromagnetic radiation energy is totally absorbed, *i.e.* when the converter is matched to the incident radiation. When there is a mismatch, part of the incident radiation is reflected, only part of the energy is absorbed, and the effectiveness is smaller than the efficiency. It is rather obvious that effectiveness is used in many experiments for simplicity, because the degree of matching is difficult to evaluate. Thermodynamics however only deals with energy efficiency.

Luminescence has been demonstrated when exposing an interface air-water to millimetre waves. This has been called the Saratov phenomenon and published (in Russian) in 1999 by Sinitsin *et al.* We follow here the description given by Chukova [35]. The conditions of exposure of the water medium to millimetre waves are the following.

1. The power density was less than 10 μW cm^{-2}, usually 1 μW cm^{-2}.
2. The millimetre wave excitation was in a sweeping mode.
3. The response of the water medium was observed in the decimetre-wave (DM) region, and measured at 0.4 and 1.0 GHz.
4. The power of this DM radiation was low, of the order of 10^{-16} W.

At higher millimetre-wave exposure level, from 10 μW cm^{-2} to 10 mW cm^{-2}, the DM radiation was not observed, while at a power level above 10 mW cm^{-2} thermal effect is observed.

A number of water media have been tested: water with NaCl, water with ice, alkaline and acid water, blood, plasma of blood, serum of blood, erythrocytes, water with narcotic, water with stimulant, mouse under narcotic, mouse under stimulant, alcohol C_2H_5OH, glycerine $C_3H_5(0H)_3$, water with NH_3 (25%), milk, white of egg, yolk of egg, etc. All these media have exhibited the DM radiation in three frequency ranges, near 50, 65, and 100 GHz. In each of these ranges there are two peaks, at 50.3 and 51.8, 64.5 and 65.5, and 95 and 105 GHz, respectively. Sinitsin *et al.* explain the existence of these two peaks on basis of the water structure.

The same decimetre luminescence has been measured on water and on human tissue: the Saratov spectrum measured on human tissue is very similar to that measured on water. One does not see how to explain such results by thermal considerations. The researchers have noted that the Saratov spectrum changes when the physiological functional condition of the tissue changes. They have deduced a new diagnosis method from this particularity, investigating the DM radiation from a body exposed to millimetre waves. Measuring the spectrum, they have also showed that abnormal tissues, like thyroid gland with diffuse toxic goitre, turn into normal ones after a certain number of sessions of millimetre-wave exposure. Hence, they consider the Saratov phenomenon not only as a diagnosis method but also as a measure of a medical treatment due to millimetre-wave exposure.

Another investigation, about possible effects of RF and microwaves on the *heart*, is also difficult to explain by a thermal effect. The location of the heart, placed quite inside of the body, combined with the small penetration of microwaves due to skin effect are such that the heart is not submitted to high microwave fields. Hearts of chicken embryos have been isolated. Heartbeat stimulation and the control effect of microwaves on the electrical activity of the heart have been analyzed. The hearts were exposed to low-power pulse-modulated microwaves at 2.45 GHz, 10 mW peak power and 10% duty cycle. The estimated incident peak power density was 3 mW cm^{-2}. The repetition frequency was within normal physiological limits (1-3 Hz). Before being exposed, the heart rhythm was rather irregular. When microwaves with a pulse repetition rate of 2.4 Hz were tuned on, the heartbeat became regular at about the same frequency. By increasing the repetition frequency, the heartbeat increased likewise until, above 2.65 Hz, the heart came back to beat irregularly. Hence, the heartbeat was synchronized with the signal from the source, within normal physiological limits [94]. This phenomenon is explained by an effect of the pulsed modulation of the source on currents due to the calcium ions channelling through the cell membrane.

VII. CONCLUSIONS

Although equipment that utilizes or emits electromagnetic energy provides benefits to mankind, it also constitutes hazards to the individual through uncontrolled and excessive emissions. There is a need to set limits on the amount of exposure to radiant energies individuals can accept with safety. These limits are still subject to change. It can be expected that adequate limits should be frequency dependent. At higher frequencies, indeed, the depth of penetration in biological tissue is limited to the superficial layers. Hence, any concern about potential hazards should focus on the tissues that are both superficial and biologically sensitive.

The limits have been quite different from one country to another in the past. In 1975 already, there was a ratio 1,000 between the US standard (10 mW cm^{-2}), and the USSR standard (10 μW cm^{-2} for an exposure time beyond 2 hours a day). Such a huge difference comes from the fact that the USSR standards took into account not only thermal but also isothermal effects. The controversy has not ceased, because accepting the possibility of non-thermal effects introduces an extra-safety factor of at least 100. Hence, the picture about protection is complicated.

In the present recommendations, two kinds of limitations are considered:

1. *Basic restrictions*, which should be always respected.
2. *Reference levels*, which could be exceeded when the basic limitations are not exceeded.

The reason is simple. The basic restrictions are expressed in quantities that are internal to the body and are not measured, like SAR. On the other hand, the reference levels are expressed in quantities that are measured *in the absence of human being*, like electric field. There are theories and estimations relating these two sets of quantities.

Only one biological effect of microwaves is well known: *heating*. Hence, the present recommendations, based only on scientific evidence, are limited to heating processes. The recommendations are based on one single source: the World Health Organization (WHO), 1993 [36]. There are, however, ambiguities in the basic texts. The document WHO 1993 states that a biological effect is produced from 1 to 4 W kg^{-1}, while calculating the safety factor from 4 and not from 1 W kg^{-1}. A further factor of 5 is recommended for the public at large, yielding safety factors of 50 and 12.5, when starting from 4 and 1 W kg^{-1}, respectively. Most documents, however, refer to a safety factor of 50. The same discrepancy is found in the document ICNIRP 1998.

The text of WHO 1993 (page 21) is based on the known effect of "increasing the body central temperature by less than 1°C when exposing healthy adults for 30 minutes to a microwave exposure of 1-4 W/kg". The safety factor has to take into account several elements: the temperature increase should be much less than 1°C; the exposure may be 24 hours a day and not 30 minutes; all adults are not healthy; there are non-adults (children); all children are not healthy; and there are "unfavorable, thermal, environmental, and possible long-term effects". Health epidemiologists have to evaluate if the safety factor is large enough.

As can be seen, establishing standards is not an easy thing to do. As an example, it is worth considering the values used in Europe for the standard related to European GSM mobile telephony, at 900 MHz, for the general public, expressed in volt per meter: (1) WHO, ICNIRP and European Union recommend not to exceed 41.2 V/m; (2) several European governments have adopted lower values, like Belgium (20.6 V/m), Italy (20 V/m, and 6 V/m for an exposure of 4 hours or more), Switzerland (4 or 6 V/m), and Luxembourg (3 V/m); (3) effects on BBB-permeability have been observed at 0.016 W/kg, *i.e.* 18 V/m; (4) considering the possibility of isothermal or microthermal effects implies an extra factor of about 100 in power, yielding 4 V/m; (5) two epidemiology studies out of four on TV/FM-exposure evidenced a two-fold increase of leukaemia under 2 to 4 V/m exposures; (6) the Belgian High Council for Health has recommended an extra safety-factor of 100 to 200, yielding 4 to 3 V/m; (7) in February 2003, the City of Paris, France, obtained from the operators not to exceed a value between 1 and 2 V/m, depending of the power transmitted at 1,800 MHz; and, more recently (8) City of Salzburg, 0.6 V/m. Hence, the picture is complex, because a number of arguments can be used, which do not lead to the same conclusions.

To get anything like a scientific conclusion on microthermal and isothermal effects, one needs to integrate electromagnetics, biology, and thermodynamics. This issue is not for tomorrow.

Medical information on exposed populations will probably yield information more rapidly.

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