Review Article

THERMAL MECHANISMS OF INTERACTION OF RADIOFREQUENCY ENERGY WITH BIOLOGICAL SYSTEMS WITH RELEVANCE TO EXPOSURE GUIDELINES

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Abstract—**This article reviews thermal mechanisms of interaction between radiofrequency (RF) fields and biological systems, focusing on theoretical frameworks that are of potential use in setting guidelines for human exposure to RF energy. Several classes of thermal mechanisms are reviewed that depend on the temperature increase or rate of temperature increase and the relevant dosimetric considerations associated with these mechanisms. In addition, attention is drawn to possible molecular and physiological reactions that could be induced by temperature elevations below 0.1 degrees, which are normal physiological responses to heat, and to the so-called microwave auditory effect, which is a physiologically trivial effect resulting from thermally-induced acoustic stimuli. It is suggested that some reported "nonthermal" effects of RF energy may be thermal in nature; also that subtle thermal effects from RF energy exist but have no consequence to health or safety. It is proposed that future revisions of exposure guidelines make more explicit use of thermal models and empirical data on thermal effects in quantifying potential hazards of RF fields.**

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INTRODUCTION

The biological effects and health hazards of radiofrequency (RF) electromagnetic fields (EMF) are the subject of a large and varied scientific literature going back to the nineteenth century, as well as ongoing discussion in the political and social arenas. Despite considerable controversy in the social arena about the possibility of hazards from chronic exposures at low exposure levels, the two major international exposure guidelines (IEEE 2006; ICNIRP 1998) are designed in large part to protect against hazards from acute exposures.

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International Commission on Non-Ionizing Radiation Protection (ICNIRP): "These guidelines are based on short-term, immediate health effects such as stimulation of peripheral nerves and muscles, shocks and burns caused by touching conducting objects, and elevated tissue temperatures resulting from absorption of energy during exposure to EMF" (ICNIRP 1998).

Institute of Electrical and Electronics Engineers (IEEE): "The development of this standard is based on the following established adverse health effects: 1) aversive or painful electrostimulation due to excessive RF internal electric fields, 2) RF shocks or burns due to contact with excessively high RF voltages, 3) heating pain or tissue burns due to excessive localized RF exposure, and 4) behavioral disruption, heat exhaustion or heat stroke due to excessive whole body RF exposures" (IEEE 2006).

In this paper, we consider the role of a mechanistic understanding of thermal hazards in setting exposure guidelines. In this context, "mechanism" is understood in a more pragmatic sense than in basic research. When devising measures for health protection, there is a need to be able to identify potential adverse effects of exposure and to predict exposure conditions that might potentially be hazardous. In this pragmatic sense, a "mechanism" is usefully defined by IEEE (2006) as a theoretical formulation that:

- can be used to predict a biological effect in humans;
- can be formulated in an explicit model using equations or parametric relationships;
- is supported by data from humans, or by animal data and can be extrapolated confidently to humans;
- is supported by strong evidence; and
- is widely accepted among experts in the scientific community.

A mechanism, in this pragmatic sense, can be used to extrapolate from animal data to humans, and predict the occurrence of adverse effects in humans over a range of exposure conditions.

We do not consider the contentious issue of hazards from low-level exposures to RF energy. No such hazards

have been proven, and for that reason none have played any direct role in the IEEE and ICNIRP exposure guidelines. The IEEE standard (p. 79) states that "All relevant reported biological effects at either low ('non-thermal') or high ('thermal') levels were evaluated. Research on the effects of chronic exposure and speculations on the biological significance of low-level interactions have not changed the scientific basis of the adverse effect level." Electrostimulation, another potential hazard mechanism, is excluded from the present discussion.

In the following section we review major thermal phenomena that are of interest in setting exposure guidelines and the current state of efforts to develop quantitative models for them. We conclude with comments on how mechanistic considerations of thermal interactions can be used to improve and extend exposure guidelines.

Heat transfer in tissue

The standard measure of exposure to RF energy is the specific absorption rate (SAR), which is the power deposited per kg of tissue, and present versions of the major guidelines specify basic restrictions in terms of SAR (either whole-body or in a particular volume of tissue). However, adverse effects of RF energy to large part depend on local increases in temperature, not the absorbed power in any particular volume. Moving from consideration of SAR to consideration of temperature changes requires an understanding of heat transport mechanisms in tissue.

Of the numerous theoretical descriptions of heat transfer in tissues that have been proposed, only one, Pennes' bioheat equation (Pennes 1948), has found widespread use in practical dosimetric studies involving RF heating of tissue. In simplified form, the bioheat equation can be written

$$k\nabla^2 T - \rho^2 C m_b T + \rho SAR = C\rho \frac{\partial T}{\partial t}, \qquad (1)$$

where

T = the temperature of the tissue (°C) above mean arterial temperature;
k = the thermal conductivity of tissue (W m^{-1} $°C^{-1}$);
SAR = the rate of electromagnetic power deposition rate (W kg^{-1});
C = the heat capacity of blood or soft tissue (W s kg^{-1} $°C^{-1}$);
ρ = the density of tissue and blood (kg m^{-3}); and
m_b = the volumetric perfusion rate of blood (m^3 kg^{-1} s^{-1}).

Extensive compilations of thermal properties of tissues are available (Chato 1985; Duck 1990; Holmes 1997); Table 1 lists ranges of values for some representative tissues. In soft tissues, the thermal conductivity, heat capacity and density are chiefly functions of water content, and the range of cited values is rather low. Tissue blood perfusion varies widely, both across tissue types and, in some tissues, with physiological condition.

The bioheat equation has been quite successful in predicting temperature increases in tissue subject to heating from a variety of sources including RF energy. However, many authors have criticized its theoretical basis. Apart from the obvious failure of eqn (1) to satisfy the law of conservation of energy, the model does not take into account the transfer of heat near blood vessels, which may include thermally important effects such as countercurrent heat exchange. One approach to remedy these problems has been to retain the bioheat equation as an empirical description, but adjusting blood perfusion parameter m_b by an "efficacy function" in the range of 0.5–1.0 to take into account countercurrent heat transfer and other effects (Brinck and Werner 1995).

Whatever its limitations, the bioheat equation has become the de facto standard approach to modeling the

Table 1. Representative values (either mean values or ranges) for thermal properties of tissues. Tissues from various nonhuman mammalian species except where indicated.

Tissue	k (W m^{-1} °C)[a]	C (J kg^{-1} °C)[b]	ρ (kg m^{-3})[b]	10^6 m_b (m^3 s^{-1} kg^{-1})[b]
Brain	0.50–0.53	3,600–3,700	1,039–1,043	7–25 7–8 (mean cerebral)
Kidney	0.49–0.54	3,600–3,900	1,044–1,050	25–125
Muscle, skeletal	0.46–0.62	3,400–3,900	1,038–1,056	0.5 (average, resting, human)
Muscle, heart	0.48–0.53	3,700 (one value)	1,060 (one value)	18–145
Liver	0.49–0.57	3,400–3,600	1,050–1,070	0.3–20
Skin	0.21–0.48	3,200–3,700	1,093–1,190	1.5–3 0.7 (human forearm, thermoneutral conditions) 3 (human forearm, hyperthermic conditions)
Spleen	0.54	3,700	1,054 (one value)	7–90
Fat	0.16–0.40	2,300–3,600	916 (one value)	3 (one value)

[a] Based on Holmes (1997).
[b] Based on Duck (1990).

heating of tissue due to absorption of RF energy. Numerical solutions of the bioheat equation, sometimes coupled with solution of the EMF equations, have been developed to predict temperature increases from RF exposure over small distance scales. These models have been applied in studies related to safety of RF exposures (e.g., Bernardi et al. 2003) or for treatment planning for hyperthermia (e.g., Sreenivasa et al. 2003). At least three commercial finite-difference-time-domain electromagnetic simulation programs are presently being extended to include solution of the bioheat equation in this way.

Thus, in the near future, it will be a routine matter to include thermal simulations, based on the bioheat equation, as an add-on to detailed calculation of the SAR pattern produced by arbitrary sources of RF energy using detailed numerical models of the human body. Such models have obvious application to design of RF exposure limits, by providing highly detailed information about the thermal consequences of exposure.

Scaling considerations. There is a need in setting exposure guidelines to choose appropriate time and distance scales over which to average exposure. This is particularly important because the electrical conductivity of tissue (and hence the SAR) varies over all distance scales ranging from molecular to centimeter dimensions, and a need to evaluate exposure over very small distance scales could lead to extremely complex dosimetry issues. Moreover, some RF sources emit pulsed energy, with high peak power but low average power, and there is a need to decide how to include temporal averaging into the design of exposure limits.

General insights into these issues can be gained by considering the analytical properties of the bioheat equation (as opposed to detailed solutions from numerical simulations of actual tissues). Numerous authors (e.g., Brix et al. 2002; Foster and Erdreich 1999; Yeung and Atalar 2001) have provided analytical solutions to the bioheat equation.

Temporal scaling and thermal averaging times. We recast eqn (1) in nondimensional form to separate effects of scale from the physics of heat transport:

$$\nabla^2 T^* - \frac{\tau_2}{\tau_1} T^* + SAR^*(r^*, t^*) = \frac{\partial T^*}{\partial t^*}, \tag{2}$$

where asterisks indicate nondimensional quantities and

$$\tau_1 = \frac{1}{m_b \rho} \tag{3}$$

$$\tau_2 = \frac{\rho C L^2}{k},$$

are time constants for convection of heat by blood flow and heat conduction, respectively, and

$$T^* = \frac{kT}{\rho SAR_0 L^2} \tag{4}$$

$$x^* = \frac{x}{L}$$

$$t^* = \frac{t}{\tau_2}$$

$$SAR^* = \frac{SAR}{SAR_0},$$

where L is a measure of the distance scale of the heating and SAR_0 is a measure of the maximum SAR in the region of interest.

In the above expressions, the time constants τ_1 and τ_2 reflect the dominant mechanism of heat transport. For heating over small distances, thermal conduction dominates heat transfer ($\tau_1 \gg \tau_2$); over larger regions convective heat transport by blood dominates ($\tau_1 \ll \tau_2$). For materials whose thermal properties are similar to those of soft tissues and with physiologically appropriate values of blood flow, the transition from conduction to convection-dominated heat transfer typically occurs over distance scales of the order of millimeters (Foster and Erdreich 1999).

In the early transient regime (for short times after the exposure has begun before effects of heat transfer become significant) the rate of rise in local temperature T in nondimensional units is simply

$$\frac{dT^*}{dt^*} = SAR^* t^* \tag{5}$$

or, in dimensioned units

$$\frac{dT}{dt} = \frac{SAR}{C}.$$

For an SAR of 10 W kg^{-1} (the maximum ICNIRP basic restriction for partial body exposure), this corresponds to a maximum rate of temperature increase of about 0.15°C min^{-1}. In the steady-state, ignoring both loss of heat to the surrounding air and heat conduction, the temperature will approach

$$T_{ss}^* \approx \frac{\tau_1}{\tau_2} SAR^*, \tag{6}$$

or, in dimensioned units

$$T_{ss} \approx \frac{SAR}{\rho m_b C}. \tag{7}$$

For an SAR of 10 W kg^{-1} and using the range of blood perfusion parameters in Table 1, this corresponds to a

steady state temperature increase of about 0.1 to 0.3°C with time constant τ_1 of approximately 1–2 min. Taking both blood perfusion and heat conduction into account, the steady-state temperature increase can be written as (Foster and Erdreich 1999):

$$T_{ss} \approx \frac{SAR}{C}\tau_{eff}, \tag{8}$$

where the effective thermal response time τ_{eff} approaches the smaller of τ_1 and τ_2.

Spatial scaling and thermal averaging volumes. The characteristics of the bioheat equation can be studied conveniently using the Green's function, which is the solution of the equation assuming a point or line source of heat. With no boundary conditions and zero initial conditions, the Green's functions for the bioheat equation are (Yeung and Atalar 2001):

$$\text{Steady-state cylindrical } G(r) = \frac{\rho_1}{2\pi k_1}K_0(\nu r) \tag{9}$$

$$\text{Steady-state spherical } G(R) = \frac{\rho_t}{4\pi k_t R}e^{-\nu R}$$

$$\text{Time-dependent cylindrical } G(r,t) = \frac{\rho_t}{4\pi k_t t}e^{-(r^2/4\alpha t)}e^{-a\nu^2 t}$$

$$\text{Time-dependent spherical } G(R,t) = \frac{\alpha\rho_t}{k_t(4\pi\alpha t)^{3/2}}e^{-(R^2/4\alpha t)}e^{-a\nu^2 t}$$

In the above expressions, K_0 is a Bessel function, ν is defined by

$$\nu = \rho\sqrt{m_b c/k},$$

α_t is the thermal diffusivity

$$\alpha_t = \frac{k}{\rho C},$$

and R and r are the distance from the point or line source of heat, respectively.

The time-dependent increases in temperature produced by an actual source of heat are found by convolving the appropriate Green's function with the SAR. The convolution operation can be considered to be a form of weighted averaging, which spreads the spatial extent of the source (the SAR pattern in the present case) by spatial extent of the Green's function. Eqn (9) yields two different length scales that characterize the distance over which this spreading occurs. These are

$$R_1 = \sqrt{4\alpha t} \approx 0.07\sqrt{t}\ \text{cm s}^{-1/2} \tag{10}$$

$$R_2 = 1/\nu = \frac{\sqrt{k_t}}{\rho\sqrt{m_b c}} \approx 0.4\text{–}0.8\ \text{cm},$$

(using the range of blood flow quoted for brain in Table 1). The first of these, R_1, is the well-known Einstein diffusion length, a measure of the distance that heat diffuses in time t. The second, R_2, is a measure of the distance at which the temperature pattern from a point source falls off due to convective cooling of tissue by blood flow.

This analysis provides some insight into the smallest distances over which variations in SAR are potentially significant. After the source has been turned on, the Green's function spreads out over a distance of the order of R_1 due to diffusion of heat. The temperature increases in tissue will consequently be smoothed out over comparable distances. For a microsecond pulse, this corresponds to a distance of about 1 μm, or roughly cellular dimensions. Unless the pulse is extraordinarily intense and brief, this precludes the need to consider variations in SAR over subcellular dimensions (at least as far as thermal mechanisms are concerned). The other distance scale, R_2, implies that the blood perfusion will smooth out the temperature response to an SAR pattern over distance scales of about 1 cm as the steady state is approached.

These considerations have important implications with respect to the possibility of "microthermal" heating of tissue from exposure to RF energy. This hypothesis was first advanced in the 1930's as an explanation for biological effects of RF energy. Schäfer and Schwan published a devastating critique of this hypothesis in 1943 on the basis of simple heat flow considerations. To illustrate, assume that a spherical object of radius R is subject to heating at a given SAR, and is surrounded by unheated material. The maximum temperature increase ΔT and thermal time constant τ_2 can be found by straightforward solution of the heat equation. Solving eqn (1) with blood flow parameter m_b set to zero yields

$$\Delta T \approx \frac{SAR}{C}\tau_2 \tag{11}$$

where

$$\tau_2 = \frac{\rho C R^2}{k}.$$

Table 2 summarizes the maximum temperature increase that would be produced in spheres of various size by heating with an SAR of 10 W kg^{-1}, assuming thermal properties similar to those of "average" brain tissue from

Table 2. Thermal response times and maximum steady-state temperature increase for spheres of different size exposed to RF energy at an SAR of 10 W kg^{-1} in an unheated medium. The thermal properties of the spheres were taken to be the mean values for brain tissue in Table 1. This shows the difficulty of creating local areas of significant temperature increase due to nonuniform SAR over small distance scales.

Radius a	Thermal response time, s	Maximum steady-state temperature increases above surrounding medium, °C
1 nm	8 ps	2×10^{-14}
10 nm	0.8 ns	2×10^{-12}
1 μm	8 μs	2×10^{-8}
1 mm	8 s	0.02
1 cm	800 s	2

Table 1. The temperature fluctuations produced by "selective" heating of small structures are clearly very small unless extreme momentary values of SAR are imposed.

Nevertheless, the "microthermal" hypothesis occasionally still surfaces. For example, Grospietsch et al. (1995), in experiments on the effect of 150 MHz RF fields on the growth rate of *E. coli*, suggested that microthermal heating of the cells, in the absence of a general temperature increase in the suspending medium, had affected the growth rate. More recently, Copty et al. (2005) proposed that changes in the fluorescence of proteins under the effect of RF exposure were caused by selective heating of the bound water surrounding the proteins. Copty et al. corrected that assumption in a later report (2006), while still arguing that some specific microwave interaction was present.

If the momentary SAR is sufficiently great, localized heating over small distance scales might nevertheless occur. An interesting example is the use of pulsed near infrared light to treat port wine stains in skin (Dai et al. 2004). The energy (from a pulsed laser) causes thermal ablation of small blood vessels without damaging surrounding tissue. Needless to say, the momentary rates of energy deposition during such treatments far exceed anything that can be achieved with ordinary RF technology.

Over somewhat larger distance scales (millimeters or more), temperature gradients can be produced by RF energy at practical exposure levels. Such temperature gradients can be both difficult to measure directly and potentially significant. For example, many investigators have used microwave energy to speed up the rate of chemical reactions, often by placing samples in modified microwave ovens (de la Hoz et al. 2005). While there have been sporadic claims over the years that these effects are in part nonthermal, no plausible nonthermal mechanism has been established. Moreover, due to inadequate dosimetry or temperature control, the studies in question have typically been inadequate to separate thermal from nonthermal effects. Adair (2003) has pointed out that relaxation times for vibrational and other excitations that might be produced in molecules by RF fields are very short (in fact, of similar orders of magnitude as thermal relaxation times), which is a strong theoretical argument against the possibility of nonthermal effects in molecules from exposure to RF energy.

Interaction of absorbed power with the human thermoregulatory system

Another thermal mechanism (in the sense defined in the IEEE standard) involves the interaction of RF energy with the thermoregulatory system, leading to a variety of physiological changes in exposed individuals. Indeed, the effect that has driven the IEEE limits for whole body exposure to RF energy, termed behavioral disruption, can be considered to be a normal thermoregulatory response in animals and not a hazardous effect at all. For example, when rats are exposed to RF energy at sufficient levels, they cease to perform an investigator-assigned task and commence to spread saliva on their tails. This effect, which is termed behavioral disruption, is a normal thermoregulatory behavior of the animals in warm environments (D'Andrea et al. 2003). The threshold SAR that results in behavioral disruption in animals is associated with a core body temperature increase of about 1°C (IEEE 2006).

Until recently, few well-controlled studies had been conducted on effects of RF energy on the thermoregulatory responses in humans. Several recent studies at the Air Force Research Laboratory at Brooks AFB, TX, by Adair and colleagues have measured thermoregulatory responses to extended (45-min) RF exposures of human volunteers under controlled environmental conditions. These studies measured a variety of sensory and thermophysiological endpoints (Adair et al. 1998, 1999, 2001, 2003; Allen et al. 2005) in subjects exposed to RF energy at frequencies of 100, 220, 450, and 2,450 MHz at levels that considerably exceeded ICNIRP and IEEE exposure guidelines. These studies are the first, and apparently only, measurements of physiological responses of humans exposed for extended periods to RF energy of substantial parts of their bodies, conducted under carefully controlled environmental conditions. The thermal responses in these subjects can be adequately modeled using a standard compartmental model for the thermoregulatory system (Foster and Adair 2004). The time scales for such responses are determined by thermoregulatory mechanisms and are in the range of tens of minutes at the SAR levels employed by Adair et al.

Table 3. Sensitivity threshold of humans and various animals to microwave and infrared radiation. The estimated temperature increase was calculated using equation 3 in Walters et al. (2000) assuming the heat conduction equation (no blood perfusion), insulated boundary conditions, and dielectric properties of skin reported by Gabriel et al. (1996). Calculations were verified by numerical solution of the heat conduction equation.

Subject	Author	Radiation	Threshold W m^{-2}	Estimated skin temperature increase °C
Human volunteers (cutaneous sensation of warmth in the middle of the back)	Blick et al. (1997)	2.45 GHz	631 ± 67, 10 s exposure	0.06
		7.5 GHz	95 ± 29 10 s exposure	0.06
		10 GHz	1 96 ± 29 10 s exposure	0.08
		35 GHz	88 ± 13 10 s exposure	0.09
		94 GHz	45 ± 06 10 s exposure	0.06
		INFRARED ($\lambda = 6$ μm)	53 ± 11 10 s exposure	
Boa constrictor	de Cock Buning (1983)	INFRARED	1.77	
Python		INFRARED	0.59	
Agkistrodon rhodostoma (pit viper)		INFRARED	0.11	
Fire beetle (*Melanophila acuminata*)	Evans (1964)	INFRARED	0.6	

There is a long tradition of quantitative analysis of effects of heat on the body, and well-established guidelines for humans in warm environments [for example, the highly regarded threshold limit value (TLV) developed by The American Conference of Governmental Industrial Hygienists]. We suggest that the thermophysical effects of exposure to RF energy on humans should be considered in the context of the much larger body of effects of heat on humans, for which a variety of quantitative models is readily available.

Perception of warmth and thermal pain

The thresholds for perception of microwave energy have been measured by Blick et al. (1997) for brief (10 s) exposure to microwave energy (2.45–94 GHz) over an area of 0.024 m^2 on the backs of human volunteers (Table 3). A thermal model shows that the temperature rise at the skin surface at the threshold for perception in these experiments is in the range of about 0.06°C over this entire frequency range. In these experiments, the threshold for perception decreased with increasing frequency because of the shorter penetration depth into tissue (and corresponding increase in SAR near the skin surface), modified by thermal conduction effects (Riu et al. 1996).

Walters et al. (2000) measured thresholds for perception of pain in human volunteers exposed to 3-s pulses of intense 94 GHz microwaves. The thresholds corresponded to a skin temperature of 43.9°C; the increases in skin temperature with RF exposure were well described by a simple thermal model (eqn 1) taking into account only heat conduction.

Thermal injury of tissue and thermal dose

The kinetics of thermal injury to tissue are characterized by an exponential relation between the time required to produce injury and the temperature at which the tissue is maintained, above a threshold of about 43°C. The thermal dose (TD) has become the standard measure used by the hyperthermia community for quantifying exposure to heat (Dewhirst et al. 2003):

$$TD = \frac{1}{60}\int R^{T(t)-43}dt. \quad (12)$$

In the above expression, $R = 2$ ($T > 43$°C) or 4 ($38 < T < 43$°C). The temperature field T is integrated over the heating period (in seconds). Thresholds for thermal damage can be conveniently expressed in terms of a related quantity, CEM43, which was defined in a classic 1984 paper by Sapareto and Dewey as the equivalent number of minutes in which tissue must be held at 43°C to produce the same thermal damage as produced by exposure for time t at temperature T. While there is considerable variability depending on the tissue and the endpoint used to assess thermal damage, values of CEM43 exceeding 10 (min) have been reported for a number of different tissues from different species (Dewhirst et al. 2003). Eqn (12) indicates (and practical experience shows) that tissues can be maintained at temperatures below 43°C for long or indefinite times without noticeable thermal damage.

Perception of thermal pain is a biological mechanism to avoid thermal injury, and evidence shows that subjects experience thermal pain from exposure to microwave energy considerably before thermal injury occurs. For example, Walters et al. (2000) measured the threshold for thermal pain from exposure to 3-s exposures to 94 GHz microwave energy in human subjects. The thresholds corresponded to a skin temperature of

43.9°C. By contrast, to achieve a CEM43 sufficient to produce thermal injury would require that the skin temperature be maintained at that temperature for several minutes. Oleson et al. (1994) reported a modeling study related to burns that a user allegedly experienced from a microwave oven whose interlocks had failed (allowing the user to place his hand in the operating oven). These investigators concluded that thermal pain would force the user to withdraw his hand before significant damage occurred. While accident scenarios might exist in which a person could sustain injury before experiencing thermal pain, such accidents would certainly require exposure levels far above present exposure guidelines.

Mechanisms related to time rate of change of temperature

Microwave auditory effect. When tissue is abruptly heated, the resulting expansion of tissue water launches acoustic waves. These waves can elicit auditory sensations in an individual whose head is exposed to pulsed RF energy, an effect called microwave hearing. For brief pulses, the magnitude P_o of the acoustic wave is of the order of

$$P_o = \frac{c_s \beta R \rho S}{CJ}, \quad (13)$$

where R is the diameter of the heated region, S is the SAR in the exposed region, β is the volumetric thermal expansion coefficient of the tissue, c_s is the velocity of sound, C is the heat capacity of the tissue, and J is the mechanical equivalent of heat (Foster and Finch 1974).

Typical experiments on the microwave auditory effect in humans involve brief (1 to 10 μs) pulses with carrier frequencies of 1–10 GHz and peak incident power densities of about 10^4 W m^{-2}. The resulting increase in temperature in the head of the subject is very small (a few microdegrees after each pulse) but the rate of heating is high (typically 1–10°C s^{-1}). The resulting sound transients exceed 100 dB peak sound pressure and are audible through bone conduction hearing. These order-of-magnitude estimates are confirmed by more detailed calculations. For example, Lin (1977) has modeled the microwave-induced sound transients in spherical models of the head. This model yields peak sound pressures that are consistent with predictions from the simple theory discussed above. The frequency spectrum of the stimulus calculated in Lin's model corresponds to the acoustic resonance frequencies of the head, also consistent with the psychophysical results.

The microwave auditory effect, as studied so far with humans, involves perception of sound stimuli that are close to the threshold for hearing. Because the conversion of thermal to acoustic energy is very inefficient and the peak sound pressure is proportional to the peak SAR, enormous peak field levels would be required to produce sound levels that might be physically damaging to tissue. Whether one views the acoustic stimuli as being undesirable is a value judgment. The ICNIRP guidelines are designed to avoid exposures that would induce audible sensations in humans. By contrast, the IEEE standard (2006) states that "The perception of a barely audible click, buzz or hiss, from pulsed radar type signals in a very quiet environment, based on real-world exposures, is not adverse to health."

Thermally-induced membrane depolarization. Wachtel and colleagues have reported (in a conference in 1984) that a single pulse of microwave energy lasting 0.1 s with a peak SAR of about 40,000 W kg^{-1} will cause a temporary cessation in the firing of the pacemaker neurons of *Aplysia*. Such a pulse will induce a temperature increase of about 1°C, at a rate of 10°C s^{-1}. The same group also reported "multiphasic body movements" in mice whose heads were exposed to intense microwave pulses at a total energy of 500–1,000 J kg^{-1} (Wachtel et al. 1990). Such pulses would produce transient temperature increases of 0.1 to 0.2°C, with a corresponding rate of temperature increase of several degrees per second. Alekseev et al. (1997) reported effects of millimeter waves on the rate of firing of snail pacemaker neurons, at an SAR of up to 4,200 W kg^{-1}, corresponding to a rate of temperature change of about 1°C s^{-1}. They attributed the effects to transient neural responses produced by the high rate of temperature increase. Similar results were reported by Brown et al. (1994).

Only preliminary theoretical models are available for this effect. Barnes (1984), based on analysis of the Nernst membrane potential, suggested that rates of temperature increase greater than about 0.1°C s^{-1} will lead to a transient change in membrane potential that is large enough to be biologically significant.

We note that very high exposures are needed to produce such effects, which would far exceed any conceivable exposure guideline. Indeed, in their experiments, Wachtel et al. placed the animals within waveguides that were connected to high-powered RF sources.

Mechanisms for "subtle" thermal effects

The question of possible biological effects of RF energy is closely linked to the question of temperature sensitivity of biological systems. Apart from the contentious issue of "nonthermal" mechanisms, RF fields at rather low exposure levels certainly do have biological effects through thermal mechanisms. These can be associated with quite small changes in temperature. We

consider some mechanisms that impart high temperature sensitivity to some biological systems.

Probably the best known example of high temperature sensitivity in animals comes from the specialized thermoreceptors of boas, pythons and pit vipers as well as many insects (Campbell et al. 2002), which aid them in hunting, feeding and overall survival. While the animals use the sensors to detect infrared (IR) energy, in all cases the sensors transform IR radiation into temperature changes, which the animals can detect with high sensitivity.

These animals achieve thermal sensitivities that far exceed sensitivity for cutaneous sensation of warmth in humans (Table 3). In part, this is due to differences in morphology: the thermosensitive membrane in the pit organs of snakes is insulated thermally by air layers on both sides, whereas human peripheral thermoreceptors are embedded in skin about 1.2 mm below the skin surface. The calculated sensitivity of the thermosensitive membrane in the pit organ of snakes is 0.003 to 0.01°C, which is roughly an order of magnitude smaller than the threshold for cutaneous perception of warmth in the human.

In many pro- and eukaryotic cells, structures exist that act, in effect, as sensitive thermometers (Glaser 2005). So-called "riboswitches," which are cytosolic proteins that regulate RNA activity (Narberhaus et al. 2006), enable bacteria and many other cells to adapt to changes in the temperature of their surroundings and other stressors. These switches induce the expression of heat shock proteins (HSPs) which (among other functions) cause cell membranes to adapt to higher temperatures by changing their lipid composition (Chowdhury et al. 2006).

Another class of thermally sensitive molecules consists of so-called TRPV-transport proteins, which are found in membranes of various cells including neurons, keratinocytes and aorta endothelial cells (Voets et al. 2004; Tominaga and Caterina 2004) (TRP stands for "transient receptor potential," V indicates a vallinoid sensitive subfamily). In mammals, TRPV3 and TRPV4 are the most important membrane channels that respond to temperature changes in the physiological range (Benham et al. 2003). They alter their conformation with a much higher sensitivity than would be possible through a simple Arrhenius mechanism. For example, between 24 and 36°C, the membrane conductance of TRPV4 channels exhibits a Q10 of 19.1 (Watanabe et al. 2002), compared with about 2 for most biochemical reactions due to the Arrhenius factor (Glaser 2000). (A Q10 of 2 means that a 10°C increase in temperature doubles the reaction rate.)

These molecular mechanisms alone are not sufficient to explain the exquisitely high sensitivity of thermoreceptors in various species, which results from information processing at many stages. Thermoreceptor cells average the information from many proteins, thermosensors at the nerve endings use the information from many thermosensitive cells, and the hypothalamus evaluates information from different thermosensors in the body. In this way, thermoreception uses a hierarchic system of reactions. On each step, however, local and particular reactions are possible (Fig. 1).

The sensation of warmth that a subject experiences while being exposed to RF energy is therefore just the endpoint of a long chain of information processing. A simple model by R. K. Adair (Adair 2001) offers an example of how a biological system might enhance its

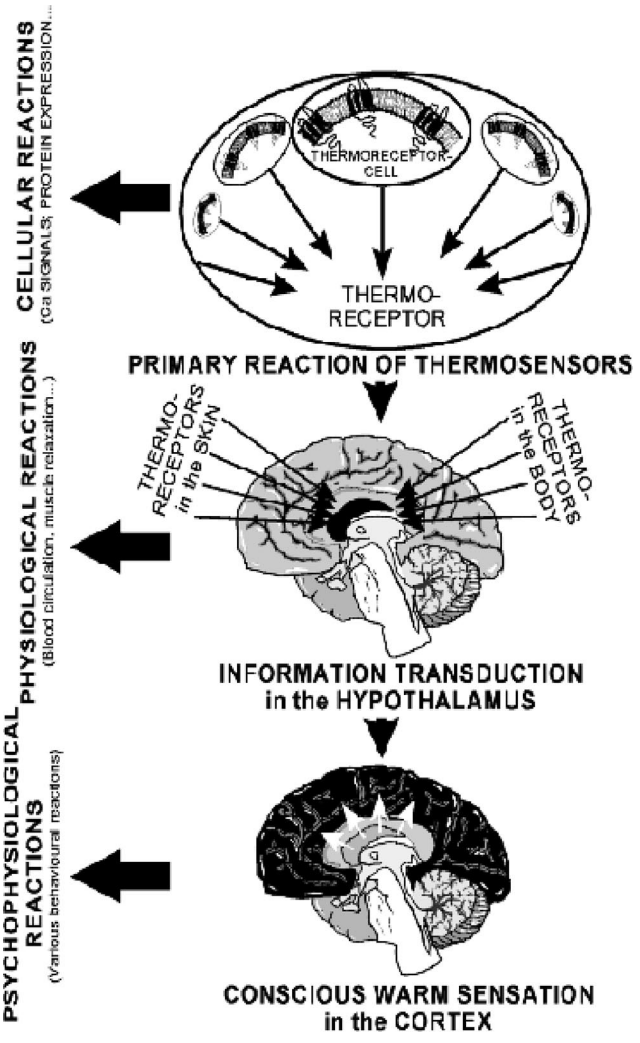

Fig. 1. A schematic illustration of the steps of thermosensation, starting from molecular reactions in thermoreceptor cells, up to the information center in the hypothalamus, leading at some conditions to conscious warm sensation. In each of these steps, filtering is accomplished to reduce noise, and each step is sensitive to physiological influences. Other thermally sensitive effects, such as variation in expression of heat shock protein or effects of thermoregulatory changes in blood flow, are possible at each stage of thermoregulation.

ability to detect small changes in neuron firing rates through the use of neural networks.

Thermal sensitivity as a possible cause of "nonthermal" effects of RF energy

The high sensitivity of biological systems to small temperature changes is an obvious factor that might lead to biological effects from rather low exposures to RF energy. It is also a potential source of difficulty in attempts to elucidate "nonthermal" effects which, depending on the system, might have a thermal basis after all.

A prominent example is the work by Smialowicz (1983), who observed physiological changes in rats and mice whose thermoregulatory systems had been impaired by drugs, subject to whole-body exposures to RF energy at 0.2 W kg^{-1} (rats) and 0.7 W kg^{-1} (mice). These exposure levels are considerably below those needed to produce behavioral disruption in these animals and are consequently of interest in setting exposure guidelines. These experiments were conducted to "determine if subtle heating by RF radiation at low power densities might be detectable in animals whose thermoregulatory response was compromised." "A re-evaluation of the literature on RF radiation-induced biological effects . . . is indicated by these studies," he concluded, and a "more prudent assessment of claims for 'nonthermal' [effects]" is needed (Smialowicz 1983).

A recent example of a subtle thermal effect is found in work by de Pomerai et al. (2000, 2006) who reported induction of heat shock proteins in the nematode *C. elegans* after extended (2 to 24 h) exposures to microwave energy. This effect was eventually found to be associated with a small (0.2°C) temperature increase in the irradiated samples (de Pomerai et al. 2006). In other experiments, Laszlo et al. (2005) observed changes in expression of heat shock proteins in cultured cells after brief (15 min) exposures to temperature increases of 1°C.

This is not to say that all reported "non-thermal" effects of RF energy are thermal artifacts, but rather that thermal and nonthermal effects can be difficult to separate experimentally. Even in the best bioeffects studies it is often difficult to control (or even measure) temperature increases in the exposed preparation with a precision less than about 0.1°C, and it would seem that many studies do much worse than that. It is clear from the above discussion that many biological processes can be significantly perturbed by temperature increases below 1°C. Some of the reported changes in the electroencephalogram (EEG) as a result of weak RF field exposure (e.g., Freude et al. 2000; Wagner et al. 2000), for example, may be caused by locally modified blood circulation in the brain, even without a sensation of warmth being perceived by the subject (e.g., Huber et al. 2005). However, such explanations are difficult to test in retrospect and other phenomena may be involved.

These thermal mechanisms are scientifically interesting and quantifiable, and can lead to biological effects at low RF exposure levels, either directly by inducing physiological changes in the body or indirectly by providing information to the subject. However, these subtle thermal effects may have no apparent health significance. The significance of small temperature-related changes observed in controlled laboratory studies need to be considered in the context of the diurnal variation in body temperature of about 1°C, increases in core body temperature of 2–3°C during sustained exercise, and variations in skin temperature of several degrees C depending on environmental conditions and the presence of clothing or other insulation.

Use of mechanistic considerations in setting exposure guidelines

The present IEEE and ICNIRP exposure guidelines are designed largely to avoid thermal hazards. Their future revisions can benefit by use of the quantitative models discussed earlier in this paper. We suggest that future needs include:

1. *Express basic restrictions in terms of temperature or thermal dose (such as TD or CEM43, defined above), instead of SAR.* This is particularly true for limits for partial body exposure, in which the total absorbed power is too small to create excessive heat loads to the body. ICNIRP has already moved in this direction. In its recent (ICNIRP 2004) statement on safety of magnetic resonance imaging (MRI) examinations, ICNIRP states "For whole-body exposures, no adverse health effects are expected if the increase in body core temperature does not exceed 1°C. In the case of infants and persons with cardiocirculatory impairment, the temperature increase should not exceed 0.5°C. With regard to localized heating, it seems reasonable to assume that adverse effects will be avoided with a reasonable certainty if temperatures in localized regions of the head are less than 38°C, of the trunk less than 39°C, and in the limbs less than 40°C." We note that these suggested limits are far below anticipated thresholds for thermal injury or excessive physiological stress; whether they are appropriate is a normative issue that we do not consider here. However, expressing RF exposure limits in terms of increases in core temperature or thermal dose or CEM43 is biologically more meaningful than expressing them in terms of SAR, at least as far as thermal hazards are concerned;

2. *Simplify the process of verifying compliance with the guidelines.* Low powered RF transmitters placed close to the body and which pose no risk of excessive heating of the body should not be subject to complex requirements for SAR testing; and
3. *Use thermal models to improve the scientific basis of the guidelines.* Thermal models based on Visible Man or other numerical models of the body are available and of demonstrated utility for predicting the heating of body tissues by RF energy. They can be used to predict the thermal consequences of many different exposure scenarios. In addition, thermal models can lead to useful predictions of thresholds for thermal injury, thermal pain, and perception of RF radiation, and to determine safety factors incorporated into exposure guidelines. This numerical work would seem to be most important in extending guidelines to protect individuals against millimeter wave radiation, for which high power sources are coming into use, and radiation in the terahertz range which is beginning to be used for imaging and other applications.

A few comments in closing: First, few injuries of any sort have been reported from exposure to RF energy. In part, this may be due to the general inaccessibility of high-powered sources of RF energy except to a few workers in a few occupational groups. This may also be due to the fact that most exposed individuals would perceive thermal pain before experiencing thermal injury and voluntarily withdraw from exposure before injury occurs. For example, medical follow up of reported cases of overexposure (above regulatory limits) to RF energy among U.S. Air Force personnel found a strong correlation between overexposure and feelings of warmth, but no signs of lasting injury (Reeves 2000). Injuries or illness from chronic exposure to RF energy at nonthermal levels, which is the subject of great public discussion, remain unproven.

Second, most reported injuries from overexposure to RF energy involve accident scenarios leading to RF exposures far above guidelines, or from failures of technology that are not directly associated with exposure to RF energy. These include numerous reported cases of burns to patients in hospitals from electrosurgical equipment and, more rarely, burns to patients undergoing MRI imaging procedures resulting from RF currents induced within the body or in electrical conductors that are in contact with the body. Other injuries (e.g., burns from superheated foods, exploding eggs, and other mishaps from use of microwave ovens) are hazards of RF technology but unrelated to human exposure to RF energy. We suggest that the most effective way to further increase the safety of RF technology would be to improve work rules and equipment design, not further refine existing exposure guidelines. As long as the guidelines are set at levels far below anticipated thresholds for thermal injury (as they are at present), the exact value of the exposure guidelines is not a significant issue.

We anticipate that the thermal models discussed above probably will not lead to strong reasons to reduce present exposure guidelines. However, they can be very helpful in clarifying the basis of the guidelines, reducing the complexity of regulatory compliance, and in extending the guidelines as new technologies come into use. To the extent that ICNIRP guidelines continue to be science-based, they should be based on as quantitative and accurate an assessment of the science as possible. We propose that future revisions of exposure guidelines make more explicit use of thermal models and empirical data on thermal effects in quantifying potential hazards of RF fields.

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