IEEE White Paper - Thermoregulatory Responses

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Introduction

In this paper, we first consider the fundamentals of human thermal physiology as the context for a synopsis of the effects of radio frequency (RF) exposure on thermoregulation. The current data that assess human responses to RF energy, collected both in the laboratory and in the clinic, will next be presented. The similar nature of heat generated in the human body by exposure to RF energy and heat generated by muscular exercise will be explored. The value of computer simulation models as predictors of human thermoregulatory responses to RF exposure will be evaluated, with reference to the unique thermoregulatory capabilities of human beings. Summarized data from animal experiments will demonstrate the general effects of many variables including, among others, field strength, frequency, polarization, whole vs. partial body exposure, and ambient conditions. These data, in turn, indicate the directions in which future studies of animals and/or people exposed to RF energy should proceed.

The ultimate goal of research involving whole-body RF exposure of intact organisms is the prediction of the effects of such exposure on human beings. Most of the published research on thermophysiological responses in the presence of RF fields has been conducted on laboratory animals, with a heavy emphasis on laboratory rodents (e.g., mice, rats, and hamsters). The large surface-area-to-volume ratio of such small mammals requires a high metabolic heat production to maintain thermal balance in the cold. On the other hand, these same small mammals are at a great disadvantage in warm environments because they lack efficient mechanisms for the dissipation of body heat. Basic information about the thermoregulatory capabilities of animal models relative to human capability is required for the appropriate evaluation and extrapolation of animal data to humans. In general, reliance on data collected on humans and nonhuman primates, however fragmentary, will yield a more accurate understanding of how RF fields interact with humans.

Fundamentals of thermoregulation

Basic concepts

Thermoregulation

Thermoregulation is the term used to describe the maintenance of the body temperature within a prescribed range under conditions in which the thermal load on the body may vary. In humans, these thermal loads come from alterations in ambient conditions (temperature, ambient vapor pressure, air velocity, clothing, and other environmental variables that may alter the temperature of the skin) and from changes in heat production
within the body. The deposition of thermalizing energy deep in the body by exposure to RF fields provides a unique exception to the energy flows normally encountered by humans, although metabolic activity in the muscles during exercise can also deposit large amounts of thermal energy directly into deep tissues. This exception has the potential to affect both heat load and systemic monitoring of heat.

Ectothermy vs. endothermy

The pattern of thermoregulation in vertebrates may be characterized as ectothermy, in which the body temperature depends on the regulated uptake of heat from the environment, or endothermy, in which the body temperature depends on a high and regulated metabolic heat production. Reptiles and a few mammals are ectothermic; they must actively seek sources of thermal energy in the environment in order to achieve some degree of thermoregulation. Most mammals and birds are endothermic, being able to generate heat in their bodies through metabolism and dissipate that heat to the environment in a regulated manner.

Normothermia

Most of the vital internal organs of thermoregulating organisms function most efficiently when they are maintained at a relatively constant temperature that is characteristic of the species. For human beings, this characteristic temperature is near 37 °C (98.6 °F). Although the temperature of individual body tissues may depart somewhat from this norm, significant departures are associated with vigorous exercise, disease states, or possibly lethal conditions. The usual range of body temperatures extends from 35.5 to 40 °C in humans and encompasses circadian variation, vigorous exercise, variations in ambient temperature, sequelae of food intake, age factors, menstrual variation in women, and emotional factors.

Behavioral and autonomic thermoregulation

Body tissues are extremely vulnerable to excessive changes in temperature, particularly to overheating. The elaborate system of mechanisms in human beings for regulating internal body temperature is therefore not surprising. In endotherms, two distinct control systems are available for thermoregulation. 1) Behavioral thermoregulation involves conscious, voluntary acts that adjust the characteristics of the air-skin interface. 2) Autonomic (or physiological) thermoregulation involves the involuntary responses of the body that generate and dissipate body heat. In humans, behavioral thermoregulation (supplemented by highly sophisticated technology) allows for survival in extreme environments, whereas autonomic thermoregulation provides for the fine control of body temperature in the resting state and is the principal control during exercise. In ectotherms, only the behavioral thermoregulatory system is available; this is described in detail by Adair (1996).

Body heat balance
Heat balance equation

The law of conservation of energy forms the basis for the study of autonomic (physiological) thermoregulation. In the steady state, heat generated in the body is balanced by heat lost to the environment such that storage of heat is minimal (cf. Bligh and Johnson, 1973). This condition can be expressed by a generalized heat balance equation:

\[ M \pm W = \pm R \pm C \pm E \pm S \]  

where

- \( M \) = the rate at which thermal energy is produced through *metabolic processes*
- \( W \) = power or the rate at which *work* is produced by or on the body
- \( R \) = the rate of heat exchange with the environment via *radiation*
- \( C \) = the rate of heat exchange with the environment via *convection*
- \( E \) = the rate of heat exchange with the environment via *evaporation*
- \( S \) = the rate of heat *storage* in the body.

All terms in equation 1 are expressed in the same units, e.g., watts. As the equation is written, negative values of \( R \), \( C \), and \( E \) may all cause a rise in body temperature; positive values may cause a fall. Work (\( W \)) is positive when done by the body (e.g., riding a bicycle), and this potential energy must be subtracted from metabolic energy (\( M \)) to find the net heat developed within the body. When \( W \) is negative (e.g., walking downhill), this energy is added to \( M \). Usually, \( E \) is positive; when \( E \) is negative, condensation occurs and thermal injury is possible.

Modes of heat transfer

No term appears in Equation 8.1 for heat transfer by *conduction*, which is usually insignificant in humans under normal conditions. However, conduction, combined with mass transfer, forms the mode of heat transfer called *convection*, a significant form of heat loss in humans. Convective heat transfer to the air is directly related to the surface area of the body, a convective heat transfer coefficient (related to air motion), and the difference in temperature between the skin and the air. The insulation value of clothing must also be accounted for.

Heat transfer by *radiation* is independent of the air temperature. The net radiant heat exchange between two objects, such as a nude person and a radiating surface in the environment, is related to their respective surface temperatures. In practice, radiant heat exchange with the environment involves estimation of the mean radiant temperature (*MRT*). Clothing complicates the analysis, as does solar heating. Exposure to RF energy provides added complications that have been analyzed by Berglund (1983).

The fourth avenue of heat exchange available to humans and many mammals is *evaporation* of water. When 1 g of water is evaporated from the surface of the body,
~2.4 kJ of thermal energy is lost. Water that is continuously lost in the expired air and water that continuously diffuses through the skin (“insensible” perspiration) account for a total heat loss of about 25% of the resting metabolic heat production \((M)\) at thermoneutrality. But, the major avenue of evaporative heat loss in humans is sweating. The efficiency of evaporative cooling depends on the vapor pressures of the ambient air and the evaporative surface and is thus a direct function of both dry bulb \((T_{db})\) and wet bulb \((T_{wb})\) temperatures. For a body under conditions of \(T_{db} = T_{wb}\) the air is at 100% relative humidity (RH) and no water can be evaporated from the skin surface. When the air is at less than 100% RH, evaporation can take place. Evaporative heat transfer from the human body depends on the evaporative area, the skin temperature, and the convective heat transfer coefficient, as well as the vapor pressures of skin and air. Clothing complicates the relationship both in terms of its insulation value and permeability.

Endogenous heat production

The basal metabolic rate \((BMR)\) is the heat production of a resting human being in a thermoneutral environment, at a time exceeding 12 h from the last meal. The standard \(BMR\) for humans is 250 ml/min of oxygen or 84 W or 0.8 MET (where 1 MET = 58.15 W/m²). 1 The \(BMR\) can be altered by changes in body mass, diet, or endocrine levels, but probably not by living in a hot climate (Goldman, 1983). In a resting human, most of the heat is generated in the core of the body (trunk, viscera, and brain), is conducted by the circulatory system to the other tissues of the body, and is eliminated from the body through the skin by the peripheral vasomotor system. The range of metabolic heat production \((M)\) for human subjects, considering activity level, physical fitness, and assorted physiological variables, is roughly 40 W/m² to 800 W/m². An increase in deep body temperature, either by heat storage or febrile disease, will produce a compensatory change in \(M\) (Shimada and Stitt, 1983); similar changes will occur if the deep body temperature rises during RF exposure (Adair, 1995). In the cold, an increase in muscle tone and piloerection can increase \(M\) by about 35%, while active shivering can increase heat production by as much as 4 to 5 times the resting level (i.e., to 160 — 200 W/m²). However, steady-state heat production in the cold will not exceed 2 times the resting \(M\), and must be supplemented by active exercise (Iampietro, et al., 1960).

Heat loss responses

Changes in vasomotor state and sudomotor activity constitute the efficient mechanisms of body heat loss in the absence of behavioral change. Fine tuning of vasodilation is the most precise and responsive method to control heat loss and retention. Sweating is a further mechanism to offload greater amounts of heat. In general, vasodilation is

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1 Traditionally, metabolism is measured in METs (1 MET = 58.15 W /m² of body surface). A normal adult has a surface area of 1.7 m², and a person in thermal comfort with an activity level of 1 MET will thus have a heat loss of approximately 100W. Our metabolism is at its lowest while we sleep (0.8 MET) and at its highest during sports activities, where 10 Met is frequently reached.
activated in thermoneutral environments, while sweating is activated in warm environments and during exercise.

Vasomotion

In cold environments, vasoconstriction of the peripheral vasculature in the skin of the trunk and extremities increases peripheral insulation and minimizes heat loss from the body core to the skin. In thermoneutral environments, when the peripheral blood vessels vasodilate, each liter of blood at 37 °C that flows to the skin and returns 1 °C cooler allows the body to lose 1.16 W·h of heat (Hardy, 1978). In warm environments, during vigorous exercise, peripheral blood flow can increase almost 10-fold, which is essential to eliminate the increased heat produced by the working muscles. The combined effect of two modes of heat transfer in the body (conduction through layers of muscle and fat, and convective heat transfer by the blood) is called tissue conductance. Conductance is thus related to the temperature difference between body core and skin.

Evaporation through sweating

Evaporation of sweat from the skin is an efficient way of losing heat, even in environments warmer than the skin. Sweating compensates for both endogenous heat production and exogenous energy absorption, including absorbed RF energy. Normal secretory functioning of the ~2.5 x 10^6 eccrine (sweat) glands in human skin is necessary to prevent dangerous levels of hyperthermia. Sweating is activated when the ambient temperature rises above 30 to 31 °C and/or the internal body temperature rises above 37 °C; local sweating rate also depends on the local skin temperature (Nadel, et al., 1971). Sweating rate is also affected by factors such as physical fitness, state of hydration, and heat acclimatization.

Thermoregulatory control

The thermoregulatory system functions as a negative-feedback control system with a reference or “set” temperature. Thermosensors are distributed around the body to provide information about the local temperature of body tissues. The thermosensors located in the skin are the most important; other sites include the medial preoptic/anterior hypothalamic area of the brainstem (locus of the “central thermostat”), midbrain, medulla, spinal cord, cortex, and deep abdominal structures. Neural signals from the sensors are integrated by a central controller, the integrated signal is compared with the internal reference, and an output command is generated to energize appropriate responses whenever a load error occurs. A negative load error (body temperature lower than set point) will increase heat production; a positive load error will increase heat loss. As detailed below, the particular effector response that is mobilized, as well as its strength, will depend on the prevailing environmental conditions.

Human heat tolerance and environmental factors

RF energy deposition
The basic problem posed by excessive body heating from any source, including absorbed RF energy, is whether the heat-loss capability of the thermoregulatory system is sufficient to prevent heat storage in the body. Thus, for a human being exposed to a RF field, Equation (1) may be rewritten as:

\[(M \pm W) + A_{rf} = R + C + E \pm S\]  \hspace{1cm} (2)

where \(A_{rf}\) represents the rate of energy absorption from the RF field. If we neglect the work factor \((W)\), the sum of the heat production, of the heat exchange by convection \((H_c)\) and radiation \((H_r)\), and of the absorbed RF energy will yield a useful estimate of the evaporative cooling required \((E_{req})\) as:

\[E_{req} = M \pm H_c \pm H_r + A_{rf}.\]  \hspace{1cm} (3)

If the maximum available evaporative cooling \((E_{max})\) is less than \(E_{req}\), \(S\) will be positive and the body temperature will rise.

Human heat tolerance

In general, the degree of body heat stress can be predicted by the simple ratio of \(E_{req}/E_{max}\), which yields a measure of the percentage of the skin surface that is wet with sweat. Values of \(E_{req}/E_{max} < 20\%\) yield a state of thermal comfort, while higher percentages indicate tolerance limits (Gagge, 1937). This same ratio has also been called the Heat Stress Index (HSI) by Belding and Hatch (1955). HSI values greater than 30\% are judged to be uncomfortable but tolerable and may interfere with concentration and fine motor performance; values from 30 - 60\% have finite tolerance times, while values from 60 – 100\% represent severe, intolerable conditions. Tolerance limits can also be determined from a standard psychrometric chart, which diagrams the ambient vapor pressure in terms of both wet-bulb and dry-bulb temperatures. A Comfort-Health-Index (C-H-I) has also been derived from such a chart and is expressed in terms of the dry-bulb temperature \((T_{db})\) at 50\% RH. Human responses change as the C-H-I ranges from 50 °C (rapid body heating, circulatory collapse, unbearable conditions) through 35 °C (“danger line” for heat stroke, slightly uncomfortable) to 20 °C (vasoconstriction of extremities, muscular pains, cold and uncomfortable sensation).

Clothing is also considered a part of the thermal environment since it presents a resistance to the flow of heat from the skin to the environment; this resistance is a direct function of the thickness of the air layer trapped by the clothing. The standard insulation unit, called the clo, was empirically derived and equals 0.155 °C m² W⁻¹ (Gagge, et al., 1941). It has been suggested (ASHRAE, 1986) that for each 0.1 clo deviation from the usual 0.6 clo insulation baseline for sedentary office workers (1MET), the air temperature for comfort can be offset by 0.55 °C; this temperature offset can be doubled if the workload is increased to 4 – 5 METs.
During exercise, the internal body temperature rises because heat generated in the working muscles is distributed throughout the body by increased blood flow. This increased blood flow, combined with peripheral vasodilation, also brings excess body heat to the surface for dissipation. In the steady state, the heat produced by moderate exercise is efficiently lost to the environment so that the internal body temperature stabilizes at an elevated level that depends primarily on the workload, whatever the ambient temperature.

During passive exposure to RF fields, thermalizing energy may be selectively deposited in specific tissue beds; the particular pattern of energy deposition varies with many physical factors of both the radiation and the target. Similarly, during exercise the source of heat lies in specific groups of muscle fibers; the particular pattern of heating varies with the activity. However, some have argued that these two scenarios may generate different thermoregulatory responses because the absorption of RF energy is “unique” (Elder and Cahill, 1984). This view limits the application of voluminous data on exercise physiology to the prediction of human thermophysiological responses to RF fields.

An early study by Nielsen and Nielsen (1965) demonstrated the equivalence of thermophysiological responses during exercise and during passive heating by diathermy. In their experiments, short-wave diathermy was used to deposit heat directly into the deep tissues of the trunk of human subjects. In other test sessions, the same subjects exercised on a stationary bicycle at a work rate adjusted so that the heat load during cycling and diathermic heating was the same (approximately 5 times the resting M or 5 METs). Four ambient temperatures (T_a), ranging from cool to warm, were studied. In the steady-state at all T_a, the rectal temperature increased by the same amount during the two procedures. Thermal conductance, assessed by changes in peripheral blood flow, and sweating rates were also comparable. Thus, passive heating by diathermy and the heat generated by active exercise produced the same kind of thermal disturbance in the body as a whole, although the distribution of heat in individual tissue compartments of the body may have been very different in the two cases. These findings indicated that the thermoregulatory consequences of whole-body RF energy deposition may be predicted by the consequences of equivalent heat loads produced by exercise.

Febrile states

The elevated body temperatures produced by exercise and those occurring during febrile disease must be differentiated. Strenuous exercise may elevate the deep body temperature to a level above the normal, regulated (or “set”) level; the magnitude of the heat loss response is directly related to this deviation as the body attempts to defend the normal level. However, during fever there is an elevation in the “set” level that is defended just as is the normal “set” level during normothermia. These differences are clearly described by Shimada and Stitt (1983).

The elevated body temperature during fever is generated differently in different T_a. In warm T_a, heat loss will be curtailed and vasoconstriction will occur; if these responses are
inadequate to increase heat storage, heat production will be increased. In cold $T_a$, greatly increased heat production, including vigorous shivering (chill), is the only way to raise the body temperature. Stitt (1979) has shown that when a pyrogenic substance is introduced into the body and the set point elevated, the thermoregulatory controller will mobilize any response appropriate to increase the storage of body heat.

Adair, et al. (1997) hypothesized that a febrile animal might utilize energy from an environmental RF field to generate a fever in response to an injection of pyrogen into the hypothalamus, thus sparing metabolic energy stores. Four squirrel monkeys were implanted with Delrin injection cannulae and re-entrant tubes in the medial preoptic/anterior hypothalamic area so that a 1 µL volume of 250 ng PGE$_1$ in saline could be injected on demand to produce a 0.6 °C fever that lasted 60-90 min. In each test, following a 90-min equilibration to $T_a = 26$ °C, the PGE$_1$ was injected and a 30-min RF exposure to either 450 or 2450 MHz CW microwaves was introduced either immediately, or 30, or 60 minutes post-injection. This procedure allowed evaluation of the potential synergism between RF energy and fever during the three different phases of the fever cycle (chill, plateau, and defervescence). Two whole-body SARs (1.5 and 3.0 W/kg) were studied at each frequency. Control conditions included 1) PGE$_1$ injection without subsequent RF exposure, 2) RF exposure following a saline injection, and 3) tests in the absence of injections and RF exposure. The major finding was that during the chill and plateau phases of the fever cycle, RF energy did indeed substitute for metabolic energy in the generation and maintenance of the fever. However, during defervescence, RF exposure tended to exacerbate the fever because sweating in this species is not sufficient to eliminate excess heat stored in the body. These responses were dose dependent and also related in complex ways to RF frequency.

**Human data from clinic and laboratory**

Humans are better equipped than any other mammal, both physiologically and behaviorally, to withstand heat generated in the body by both exogenous and endogenous sources. Thermalizing energy deposited in the body during RF exposure should be no exception. A recent summary by Mantiply, et al. (1997) details the range of RF field levels that are associated with a variety of environmental and occupational sources. An earlier Tell and Mantiply (1980) study of 486 locations within 15 metropolitan areas of the United States estimated that more than 99% of the population is exposed to background RFR at less than 1 µW/cm$^2$. At the resonant frequency for humans, this represents a whole-body SAR of 0.0004 W/kg, or about 0.03% of the normal resting $M$. This is a completely insignificant amount in respect of thermoregulation. Even the whole-body SAR of 0.4 W/kg, adopted as the basis for controlled or occupational exposure in many exposure guidelines, represents only 35% of the resting $M$. This is equivalent to the heat retained by donning a light sweater and is small enough to be unnoticeable and of little or no physiological significance during most daily activity.

Thermoregulatory processes are ongoing in each of us all of the time. Small perturbations in endogenous heat production or in the thermal characteristics of the environment result in finely-tuned adjustments in one or more of the thermoregulatory...
mechanisms discussed above. The remarkably stable internal body temperature, with its
circadian rhythm, is the result. Most young and healthy humans have the capacity to cope
with exercise or work loads that are up to 15 times the resting \( M \) even when taken in
thermally stressful environments. The exceptional rates of human sweat production,
coupled with efficient behavioral thermoregulation, maintain a minimal rise in deep body
temperature. This is consistent with recent reports of humans exposed to modest levels of
RF fields in laboratory or clinic, which show only expected physiological responses and
have not identified any adverse health effects. For the purposes of setting exposure
guidelines, these physiological effects are regarded as biological effects and not health
effects, as they are part of the normal mechanisms of thermal homeostasis

Use of RF energy for re-warming

In addition to the extensive use of microwave energy in both diathermy treatments and
in localized hyperthermia as an adjunct to cancer treatment, techniques are also under
development that use RF energy for re-warming from hypothermia, both whole-body and
partial-body. Studies on anesthetized rhesus monkeys (Olsen and David, 1984; Olsen, et
al., 1987) explored the potential usefulness of a 13.56 MHz RF induction coil vs a
surgical heating pad to provide rapid re-warming from both moderate (\( T_{re} = 28 – 30 \) °C)
and severe (\( T_{re} < 20 \) °C) hypothermia in Rhesus monkeys. Heart rate, respiration rate,
blood pressure, and \( T_{re} \) were monitored continuously during treatment, while serum
enzyme levels were monitored before, during, and up to 48 h after treatment. A post-
treatment rise in serum enzyme levels, peaking at 24 hours, was noted for both re-
rewarming methods and ascribed to thermal effects. RF heating at low power (60 W) was
judged superior to the heating pad in restoring normothermia, and also more efficient
than a loop device (Magnetrode) used to re-warm hypothermic dogs (White, et al., 1984).
A similar 13.56 MHz trunk coil, which provided RF warming to mildly hypothermic
male subjects, was found to restore normal body temperature more rapidly than the
conventional methods of warm water immersion or use of a sleeping bag (Hesslink, et al.,
1989). Special RF coils developed to resonate at 27.12 MHz have been used to warm
divers’ cold hands and feet (Olsen, 1990; Lloyd and Olsen, 1992). Not only were skin
areas remote from the coils warmed by heated blood, but also no adverse thermal effects
were observed during these procedures.

Human overexposure data

Chiang and Shao (1989) reported that “hundreds of male volunteers” in China have
received RF irradiation as a contraceptive procedure. A group of 53 volunteers was
treated with 2450 MHz energy localized to the testes once a month for 30 minutes (Fang,
et al., 1982). If the testes were heated to 40 – 42 °C, sperm counts were reduced to
<5x10^9/L by 7 weeks after the first irradiation and persisted at this level. Neither a
change in sexual function nor deleterious side effects were reported. However, no data
were presented on the effectiveness of the treatment as a contraceptive and there was a
suggestion that the near field exposures used provided inhomogeneous exposure to the
testes. A more recent study, reporting a similar attempt to use RF energy to induce
temporary sterility in adult males, also gave data related to the thermal effects of long-
term, partial-body exposure at high intensities (Liu, et al., 1991). Thirteen male
volunteers underwent localized RF exposures of the testes at 915 or 2450 MHz in weekly
sessions that lasted 30 min each. Irradiation was carefully restricted to the testes. Power
levels were 20 to 30 watts, sufficient to raise the scrotal skin temperature 10 °C above its
normal level. Seven subjects received over 100 such sessions, the remainder somewhat
fewer. Six months after termination of the exposures, biopsies of testicular tissue were
taken for microscopic examination. While considerable cellular damage was evident, no
significant gross morphological abnormalities were found. Further, despite evidence of
greatly reduced spermatogenesis during the treatment, sterilization was not reliably
achieved by this method, as two of the men fathered children during the course of the
study. A major conclusion was that human testicular tissue appeared much more resistant
to thermal injury than equivalent tissue in experimental animals, such as similarly-
exposed rats or rabbits.

Other data on RF overexposure of human beings in the military and/or industrial
environments have been collected over the years. A report by Mitchell (1985) indicated
that over the preceding 10 years, 300 reported overexposure incidents were investigated.
Of these, 58 were confirmed overexposures, the remainder being within the permissible
exposure limit (PEL) of 10 mW/cm² in any 6 min period. Of the 58 overexposures, most
of which were in the frequency range between 1.5 and 10 GHz, 45% of the individuals
felt a clear warming sensation and terminated the exposure within less than 6 min. The
power densities ranged from 15 to 160,000 mW/cm² (with most between 40 and 1000
mW/cm²) and nearly all were partial-body exposures. The clinical findings of the
overexposure victims were inconsistent, even for intense localized exposure. Erythema
and/or edema were rarely found. Abnormalities in the lens of the eye that were noted
were not associated with visual impairment. Follow-up tests of serum enzyme levels,
bleed counts, blood pressures, sedimentation rates, and EKGs were all clinically
unremarkable. Unfortunately, a nearly complete lack of pre-exposure baseline data
hampered the evaluation of any abnormal findings.

Laboratory studies of human volunteers

Adair, et al. (1998) reported the first in a series of studies in which human volunteers
were exposed to plane wave RF fields at controlled power densities in highly controlled
thermal environments. Thermoregulatory responses of heat production and heat loss
were measured in seven adults (4 females and 3 males, aged 21 to 57 yr) during 45-min
dorsal exposures of the body to 450 MHz CW RF fields. Two power densities, measured
on the antenna boresight in the center of the subject’s back (local peak PD = 18 and 24
mW/cm²; local normalized peak SAR = 0.32 [W/kg]/[mW/cm²]) were tested in each of
three ambient temperatures (T_a = 24, 28, and 31 °C), plus T_a controls (no RF). No change
in metabolic heat production occurred under any of the exposure conditions. Vigorous
increases in local sweating rate on the back and chest, directly related to both T_a and PD,
cooled the skin and ensured efficient regulation of the deep body (esophageal)
temperature to within 0.1 °C of the normal level. Category judgments of thermal
sensation, comfort, sweating, and thermal preference usually matched the measured
changes in physiological responses and skin temperatures (Adair, et al., 1999a). At the
highest local PD explored (24 mW/cm²), the normalized peak surface SAR was 7.7 W/kg. This PD exceeds the 20 mW/cm² allowed for partial-body exposure by the IEEE/ANSI C95.1 (1992) standard (at 450 MHz) for a controlled environment, and is six times the comparable standard for an uncontrolled environment. Nevertheless, the study demonstrated that, even under ambient conditions that were often judged uncomfortable and thermally stressful, the internal body temperature of the volunteers was regulated with precision by the mobilization of appropriate autonomic heat loss responses, principally sweating.

A second study (Adair, et al., 1999b) compared the results described above with those collected on a second group of human volunteers, exposed to RF energy at 2450 MHz CW energy. The basic protocol was identical, as were the ambient temperatures and response measures, with the addition of local skin blood flow at 3 sites on the body. The normalized peak SAR, measured at the location of the subject’s center back, was the same for comparable PD at both frequencies, i.e., peak surface SAR = 6.0 and 7.7 W/kg. As in the first study, no change in metabolic heat production occurred under any exposure conditions at either frequency. The magnitude of increase in those skin temperatures under direct irradiation was directly related to frequency, but local sweating rates on back and chest were related more to Tₐ and SAR. Both efficient sweating and increased local skin blood flow contributed to the regulation of the deep body (esophageal) temperature to within 0.1 °C of the baseline level. At both frequencies, normalized peak SARs in excess of IEEE/ANSI C95.1 (1992) guidelines were easily counteracted by normal thermophysiological mechanisms. The observed frequency-related response differences agree with classical data concerning the control of heat loss mechanisms in human beings.

A third report in this series (Adair, et al., 2001a) compared the thermophysiological responses of human volunteers to 2450 MHz CW and pulsed (PW) fields of equal average power density. The two experiments were conducted 1.5 years apart. The subjects in the 2450 MHz CW experiment were 7 adults (two females, five males of age range 41-68 years); those in the 2450 MHz PW experiment (65 µsec pulse width, 10⁴ pps) were 6 adults (three females, three males of age range 36-68 years). Physiological responses of heat production and heat loss (esophageal and six skin temperatures, metabolic heat production, local skin blood flow at 3 sites, local sweat rate at 2 sites) were measured under the standardized protocol (30 min baseline, 45 min RF or sham exposure, 10 min baseline) in three ambient temperatures (Tₐ = 24, 28, and 31 °C). At each Tₐ, average power densities (PD) studied were 0, 27, and 35 mW/cm²; equivalent local peak SAR was 0, 5.94, and 7.7 W/kg. Mean data for each group showed minimal changes in core temperature and metabolic heat production for all test conditions and no reliable differences between CW and PW exposure. Local skin temperatures showed similar trends for CW and PW exposure that were PD-dependent; only the skin temperature of the upper back (facing the antenna) showed a reliably greater increase (P=.005) during PW exposure compared with CW exposure. Local sweat rate and skin blood flow were both Tₐ- and PD-dependent and showed greater variability than the other measures between CW and PW exposures; this variability was attributable primarily to the characteristics of the two subject groups. With the one noted exception, no clear
evidence for a differential response to CW and PW fields was found, confirming extensive data collected earlier on squirrel monkeys (Adair, et al., 1993).

An extension of the peak power density (PD = 35 mW/cm²) studied previously at 2450 MHz by Adair, et al., (1999b) has been recently reported (Adair, et al., 2001b). During partial-body exposures of 7 human volunteers, two additional peak PD were tested (50 and 70 mW/cm²). The higher of these PD, with a normalized peak local SAR of 15.4 W/kg, was well outside the IEEE C95.1 (1999) guidelines for partial-body exposure, as was the estimated whole-body SAR ~ 1.0 W/kg. The subject volunteers, identical to the original group save one, were tested at each PD in 3 \( T_a \) (24, 28, and 31 °C) under the standard protocol described above. The thermophysiological data (esophageal and 6 skin temperatures, metabolic heat production, local sweat rate, and local skin blood flow) were combined with comparable data at PD = 0, 27, and 35 mW/cm² from the 1999 study to generate response functions across PD. No change in esophageal temperature or metabolic heat production was recorded at any PD in any \( T_a \). At PD = 70 mW/cm², skin temperature on the upper back (irradiated directly) increased 4.0 °C in \( T_a = 24 °C \), 2.6 °C in \( T_a = 28 °C \), and 1.8 °C in \( T_a = 31 °C \). These differences were primarily due to the increase in local sweat rate, which was greatest in \( T_a = 31 °C \). Also at PD = 70 mW/cm², local skin blood flow on the back increased 65% over baseline levels in \( T_a = 31 °C \), but only 40% in \( T_a = 24 °C \). Although \( T_a \) becomes an important variable when RF exposure exceeds the C95.1 partial-body exposure limits, vigorous heat loss responses of blood flow and sweating maintain normothermia efficiently. It is also clear, from subjective responses by the subjects, that strong sensations of heat and thermal discomfort will motivate a timely retreat from a strong RF field long before these physiological responses are exhausted.

Clinical data of humans exposed to MRI

The exposure of patients to the magnetic resonance imaging (MRI) environment at 64 MHz may produce heating of body tissues that is related to the changing fields of the RF coils. A considerable literature describes thermoregulatory responses of humans to those fields during a variety of MRI procedures. The data have been collected primarily in the clinic, rather than in the laboratory. An early study (Kido, et al., 1986) measured blood pressure, heart rate, respiration rate, and axillary temperature in 27 volunteer during MRI scans of both trunk and head at 1.5T and two RF power levels. In recent studies, more attention has been paid to equilibration of the patients prior to MRI scans, control of ambient conditions, specification of SAR, and assessment of several physiological variables. Shellock and Crues (1988a, b) measured skin, sublingual, and corneal temperatures of 35 patients during MRI with a head coil (1.5T at 64 MHz). The estimated peak SARs ranged from 2.54 to 3.05 W/kg. An average corneal temperature rise of 0.5 °C (range = 0.0 to 1.8 °C) was statistically significant (P< 0.001) as were slight elevations in the skin temperature of head regions (P < 0.01) compared to pre-scan levels. No change was measured in sublingual temperature after scans of at least 8 minutes duration. In another study (Shellock, et al., 1989a), sublingual and skin temperatures were measured with Luxtron fiberoptic probes in 6 subjects before (20 min), during (30 min), and after (20 min) MRI in a 1.5T body coil at SARs from 2.7 to 40 W/kg. Skin
blood flow (SkBF) was measured with a laser-Doppler flowmeter. Although the 30-min
scans were insufficient to establish a thermal steady state, the measured temperature
changes (e.g., a maximal rise of 0.1 °C in sublingual temperature) were not significantly
different from zero. The scans produced primarily surface heating, with increases in
SkBF that were significantly different from the pre-scan level only at the 30th minute.
The authors stated that the changes in tissue temperature were “physiologically trivial and
easily tolerated by the subjects” (op. cit., p. 904). Scrotal MRI of 8 men at 1.5 T (range
of whole-body SAR from 0.56 to 0.84 W/kg) and an average duration of 23 min produced
a maximal rise of 3.0 °C in scrotal surface temperature (Shellock, et al., 1990). The
authors claimed that this elevation in temperature was well below the threshold for a
reduction in spermatogenesis, according to an analysis by Berman (1984).

That measured tissue temperature changes during MRI are attributable to RF exposure
during the procedure was demonstrated by experiments in which 6 male subjects were
exposed to 1.5T static magnetic fields only (Shellock, 1992; Shellock, et al., 1989b).
Sublingual temperature and several skin temperatures were measured during 20-min
scans that followed a 20-min equilibration to an ambient temperature of 21 °C. No
change from the equilibrated level occurred in any measured body temperature during the
scans. The authors stressed the importance of careful control over environmental and
circadian variables during such experiments. The general conclusion to be drawn from
data collected on subjects undergoing MRI at 1.5T, under ambient conditions typically
found in the clinic, is that tissue temperature changes are small and far below hazardous
levels (Shellock, 1992). In a review, Gordon (1992) concluded that if the ANSI 1982
exposure limit of 0.4 W/kg is applied to MRI procedures, the resulting elevations in body
temperature will be well below the FDA guidelines of 1.0 °C for brain tissue, 2.0 °C for
the torso, and 3.0 °C for the extremities. He stated that while SARs up to 2.0 W/kg may
produce significant elevations in core and skin temperatures, these “…are slight and
appear to be quite safe” (op.cit., p.282).

MRI exposure data (laboratory studies of animals)

As an adjunct to the human data, a study was undertaken to measure the thermal effects
of MRI on 12 anesthetized, fleeced sheep (Barber, et al., 1990). Exposures occurred in a
1.5 T MRI system using quadrature, circularly-polarized field (vector) excitation for
whole-body scans and a head coil for scans of head only. Subcutaneous temperatures
(abdomen, chest), vena cava and rectal temperatures were monitored during body scans
(SAR = 1.5 to 4.0 W/kg) of 20 to 104 minutes duration. Other temperatures measured
during head scans (SAR = 4.0 W/kg) included cornea, vitreous humor, head skin, and
jugular vein. Five animals exposed at 4.0 W/kg (head or whole body) were allowed to
recover from the procedure and exhibited neither incipient cataracts nor ill health (as
determined by a veterinarian) 10 weeks later. Controls consisted of pre-scan "control
periods" of variable duration. During whole body scans of 4.0 W/kg, rectal temperature
rose at a rate of about 0.023 °C/min; vena caval temperature rose at a slightly higher rate.
SARs less than 4.0 W/kg produced proportionately lower rates of temperature increase.
Temperature elevations in eye or cornea during a 60-min head scan at 4.0 W/kg did not
exceed 1.5 °CIn this study, behavioral thermoregulation was disabled by anesthesia,
panting was prevented by controlled ventilation through an endotracheal tube, and heat loss by convection and radiation was compromised by the intact fleece. These constraints prevented attainment of a steady state during the scan (i.e., body temperatures continued to rise). Although the exposure conditions were generally in excess of those used routinely in the clinic, the measured elevations in body temperature were insufficient to cause adverse thermal effects.

MRI exposure data (laboratory studies of humans)

A study by Schaefer (1988) involved 20-min whole-body MRI scans (SAR = 4.0 W/kg) of 11 adult volunteers. The scan was preceded and followed by 20-min baseline periods. Measured variables included esophageal temperature, assorted skin temperatures (including forehead, xiphoid, abdomen, and genital areas), metabolic heat production, heart rate, respiration rate, and blood pressure. Although the initial baseline period was insufficient to produce a steady state, no change in the group mean esophageal (deep body) temperature was noted until the end of the 20-min MRI scan when the increase was 0.3 °C (P<.005). At the end of the scan, skin temperatures near the isocenter of the scanner had risen by as much as 3 ± 0.5 °C, but these increases were judged to be non-hazardous. Blood pressure, measured 20 min before and after the scan did not change but slight elevations were recorded in heart rate and respiration rate that were not statistically significant. In general, this study and that of Shellock, et al. (1989b) indicate that MRI scans at whole-body SARs as high as 4.0 W/kg do not produce significant changes in deep body temperature and that surface temperature elevations are within the normal variation produced by changes in T_a or that occur during normal activity. It is important to note, however, that the MRI exposure environment is atypical. The penetrating RF field is primarily magnetic, with a small contribution from the electric field (Bottomley, et al.1985); thus, the ohmic heating that occurs is greatest at the surface and least at the center of the body.

A more recent report (Shellock, et al. 1994) describes 16-min. MRI exposures of 6 human volunteers in a body coil at 1.5 T, 64 MHz. Subjects were equilibrated to a T_a = 21.3 - 23.3 ± 0.4 °C for about 15 min prior to the exposure. Tympanic membrane temperature was recorded immediately before and after the MRI exposure, and heart rate, oxygen saturation, skin blood flow, and 6 skin temperatures were recorded at 2-min intervals during the whole procedure. The report states that RF exposure was at a calculated whole-body SAR of 6.0 W/kg, achieved by use of a "prototype pulse sequence". The authors reported statistically significant (P < .05) increases in tympanic and 5 skin temperatures, heart rate, and skin blood flow. These changes were not considered deleterious to the subjects and such a high SAR appears to be well tolerated by persons with normal thermoregulatory function. However, the report suffers from a lack of technical detail with respect to the purported whole-body SAR achieved, notwithstanding several references.

As a test of a modeling effort (see below), Adair and Berglund (1992) reported the results of tests on two normal male subjects who underwent a series of three 20-min MRI scans (1.5T) of the trunk at a whole-body SAR of 1.2 W/kg. Each session began with a
30-min equilibration to the ambient conditions ($T_a = 22 \pm 1$ °C, minimal air movement) and successive 20-min scans were separated by a 35-min re-equilibration period. Esophageal temperature and several skin temperatures were monitored continuously with Luxtron fiberoptic probes, as was sweating rate from chest and thigh. Judgments of thermal sensation and discomfort were obtained periodically throughout each test. For both subjects, skin temperatures of chest and thigh increased 1.1 °C during each scan. At the same time, the esophageal temperature was very stable throughout the 170 minutes of the test session, varying at most 0.3 °C from the initial level. This stability occurred despite an overall rise of about 2.5 °C in skin temperatures and periodic sweating of significant magnitude on both sites sampled. There was little, if any, recovery of pre-scan body temperatures between successive scans. As the test session progressed, both subjects reported increased sensations of warmth that were directly related to the increased skin temperatures.

Predictions based on simulation models of physiological responses

Multiple-node models

The modeling of physiological responses becomes important when its purpose is to simulate experiments that cannot be performed or to extrapolate variables that are not attainable through experiment. The basis of thermophysiological modeling is the energy (heat) balance equation (1). These models incorporate the physical characteristics of the body, the heat production and heat loss responses, and all relevant environmental parameters, many of which have been discussed here. In such models, absorbed RF energy is added to metabolic energy and must be balanced by appropriate heat loss responses in order to prevent heat storage in the body.

A model by Stolwijk and Hardy, first published in 1966, updated by Stolwijk (1971) and Stolwijk and Hardy (1977), has often been used as the basis for predicting the possible thermoregulatory outcomes of RF energy deposition in selected parts of the human body. The model was used, for example, to simulate the deposition of 100 watts of RF energy into the core compartment of the head for 30 min in a thermoneutral $T_a$ of 30 °C (Stolwijk, 1980). This simulated exposure caused only a small increase in brain temperature because of the high rate of brain blood flow and the mobilization of strong heat loss through sweating. Because heat loss far exceeded heat production plus RF energy input, all body temperatures were predicted to fall. Attempts by others to improve on this model have had varying degrees of success that have been described elsewhere (Adair, 1995).

Predictions of a two-node model

A simpler model of physiological thermoregulation has been adapted to predict the consequences of human exposure to RF fields in the MRI environment (Adair and Berglund, 1986). The model has only 2 nodes (core and skin) but in most other respects is similar to the Stolwijk and Hardy formulation, including a basis in the heat balance equation. It predicts physiological heat loss responses in real time in terms of $T_a$, air
movement (v), and whole-body SAR. Assuming a criterion elevation in deep body temperature (?T<sub>co</sub>) of 0.6 °C, T<sub>a</sub> = 20 °C, and v = 0.8 m/sec, the model predicts that a 70 kg patient could undergo a MRI scan of indefinite duration at SAR = 5 W/kg. Lowering T<sub>a</sub> or increasing v permits a rise in lower permissible SAR for a given ?T<sub>co</sub>. More strict ?T<sub>co</sub> criteria result in lower permissible SARs and shorter exposure durations. The limiting response is usually the rate of peripheral blood flow, although sweating can play a role in limiting ?T<sub>co</sub>.

Restrictions on the rate of skin blood flow (SkBF), ranging from 0 to 89% of normal, have also been studied with this model (Adair and Berglund, 1989). Model predictions indicated that restrictions of up to 67% of SkBF would yield a tolerable ?T<sub>co</sub> (= 1 °C) during MRI scans (SAR = 4 W/kg) of 40 min or less under normal clinical conditions. Increased T<sub>a</sub> and RF exacerbate the thermal stress imposed by absorbed RF energy, while severely impaired SkBF encourages short MRI exposures (20 min or less) at SAR = 3 W/kg.

After generating predictions based on many values of each parameter, a nomogram was developed based on the fact that, at any given T<sub>a</sub>, a person can absorb some level (SAR) of RF energy indefinitely; i.e., achieve thermal equilibrium with the prevailing conditions. When SAR is low, T<sub>co</sub> will rise initially and then stabilize at an elevated level. If SkBF is impaired, the maximal SAR at which thermal equilibrium can be attained will be lower. Figure 1 shows the maximal SAR for equilibrium in two T<sub>a</sub> (20 and 27 °C) as a function of the impairment in SkBF. The solid line defines the limit of the zone of stable T<sub>co</sub> at T<sub>a</sub> = 20 °C; the dashed line defines the same limit for T<sub>a</sub> = 27 °C. Thus, raising the T<sub>a</sub> by 7 °C decreases the maximal SAR for equilibrium by ~1 W/kg. If the SAR under consideration exceeds the maximal value for thermoequilibrium, a continuous rise in T<sub>co</sub> can be expected during RF exposure. The model predicts that the rate of this increase will depend on the impairment in SkBF, the T<sub>a</sub>, the RH, and the clothing insulation (clo). Adair and Berglund (1989) provided explicit corrections to the predictions of their model as a function of departure of SkBF, T<sub>a</sub>, RH, and clo from those specified in Figure 1.

Schaefer (1992) has used these predictions to calculate the effect of T<sub>a</sub> during a 60-min MRI scan on the average rate of increase of T<sub>co</sub> under conditions of 40% impairment of SkBF and clo = 0.2. He calculated, for example, that a scan at SAR = 4 W/kg would result in a ?T<sub>co</sub> of only 1°C when T<sub>a</sub> = 19 °C. Further, a 1-hr RF exposure to SAR = 1 W/kg, even at T<sub>a</sub> = 27 °C should result in no rise in body temperature. These predictions do not conflict with clinical data, nor with ongoing laboratory studies of human volunteers (Adair, et al., 1998, 1999a,b, 2001a, b).

Other predictions of the 2-node model indicate that pre-cooling of patients to the prevailing T<sub>a</sub> prior to a MRI scan has little value in preventing a rise in body temperature; further, use of a blanket (increased clo) should be discouraged in the clinic (Adair and Berglund, 1992). Tests of two normal male subjects, described above, provided further justification for the model's predictions. However, the authors pointed out clearly the limitations of the 2-node model; the predictions are based on whole-body RF exposure,
an atypical situation for the MRI clinic. A model having many more nodes (e.g., Stolwijk, 1971) would be much more useful for general predictions of human responses to RF energy absorption.

**Human thermal sensation of RF energy**

Since RF exposure generates heat in body tissues, such energy can be part of the thermal environment to which humans and animals may potentially be exposed.

Although physiological responses (e.g., sweating) may be initiated automatically by thermal stimuli, the sensation of tissue warming is necessary to initiate appropriate behavioral action. The stimulation of temperature-sensitive nerve endings located within the outermost 0.6 mm of mammalian skin probably underlies the sensations of changes in skin temperature (Hardy and Oppel, 1937). Whether or not RF exposure produces a warmth sensation depends on many parameters of the signal, e.g., frequency, modulation intensity, duration, as well as the body locus and the exposed surface area. Many of these parameters influence the magnitude of thermal sensations derived from exposure to infrared (IR) radiation (Stevens, 1983). IR energy is absorbed in the most superficial layers of skin in close proximity to the temperature-sensitive nerve endings; a similar absorption profile should be obtained for the higher microwave frequencies (10 GHz and above). However, lower RF frequencies will be absorbed in complex patterns at other depths, making prediction of thermal sensation difficult.

**Thresholds**

Archival data

Absolute thresholds for the detection of RF irradiation by human observers were determined in several archival studies (Schwan, et al., 1966; Eijkman and Vendrijck, 1961; Vendrijck and Vos, 1958; Hendler, 1968; Hendler and Hardy, 1960; Hendler, et al., 1963). All of these studies involved brief exposures (10 sec or less) and restricted areas of forehead or forearm skin. In general, the shorter the wavelength of the irradiation, the less energy was required to provoke a just-detectable sensation of warmth (Michaelson, 1972). When a 37 cm² area of forehead was irradiated for 4 sec, the mean absolute threshold of warmth was 33.5 mW/cm² at 3 GHz, 12.6 mW/cm² at 10 GHz, and 4.2 mW/cm² at frequencies > 1000 GHz (far-IR). Irradiation of small areas of skin by 3 or 10 GHz pulsed (0.4 µsec pulse width, 2500 pps) microwaves had to last at least 5 sec in order for the minimal intensity to evoke a thermal sensation and the exact intensity depended on the area stimulated. At shorter stimulus durations, the intensity had to be greatly increased to evoke comparable warmth sensations. This phenomenon is called temporal summation and the shortest duration at which only intensity matters is called the "critical duration" (Stevens, 1983).

Justesen, et al (1982) incorporated indirect assessment of absorbed RF energy during 10-sec exposures of the human forearm (average area = 107 cm²) to 2.45 GHz CW fields. Warmth sensations were reported when the energy density of the RF field was ~29 mJ/cm², compared to ~1.8 mJ/cm² when the same skin area was exposed to far-IR.
radiation. These thresholds corresponded to power densities of 27 and 1.7 mW/cm² and, thus, were similar to results reported in the earlier studies cited above.

Recent extensions of classical data

Blick, et al (1997) measured the threshold for thermal sensation across a range of five RF frequencies from 2.45 to 94 GHz plus far-IR (~3000 GHz). Judgments of threshold warmth sensation, across a skin area of 327 cm² centered on the subject's back, were determined at each frequency using a double-staircase psychophysical procedure. The stimulus duration was 10 sec and the interstimulus interval was 1 minute. Thresholds were determined at each frequency for a group of 16 adult male volunteers. Thresholds of warmth were a linear function of frequency when the data were plotted in log log coordinates. The threshold at 2.45 GHz (63.1 ± 6.7 mW/cm²) was more than an order of magnitude larger than that measured at 94 GHz (4.5 ± 0.6 mW/cm²); in turn, the latter was not significantly different from the IR threshold (5.34 ± 6.7 mW/cm²). In general, measured warmth thresholds reflected the skin depth at each frequency and a theoretical analysis (Riu, et al., 1997) suggested that a constant temperature increase of ~0.07 °C at or near the surface of the skin was the adequate stimulus for perception. This analysis also indicated that the depth at which the thermal receptors are located is not a relevant parameter, as long as it is within 0.3 mm of the surface.

Suprathreshold functions including pain

No new data on pain sensations derived from RF exposure have appeared in the literature since the classical studies of Cook (1952 a,b), although these early data should be confirmed and extended. Cook investigated the potential of 9.4 and 10 cm microwaves to induce pain sensation in two exposure areas (53.2 and 9.5 cm²) of human skin (forearm, thigh, and calf). The subject was instructed to report when a burning pain sensation occurred and the latency to report was noted. The temperature of the skin at pain threshold was measured with a copper/constantan thermocouple held at the center of the irradiated surface. The final skin surface temperature at pain threshold was 46.1 ± 1.0 °C. Cook concluded that the pain threshold, aroused by microwave irradiation, was directly related to the skin temperature. However, the power density of the radiation at threshold could depend on area exposed, exposure time, initial skin temperature, anatomical site, and thermal conductivity. Cook provided a theoretical analysis based on thermal flow theory that explained the results measured with short exposures. Longer exposures had to involve vasomotor responses in the capillaries, a conclusion also reached by Riu, et al. (1997) for the adequate RF stimuli for the sensation of warmth.

[Any Blick data to add?]

Supporting data from animal studies/physiological responses

Threshold effects

For any given species, under any given environmental conditions, an intensity of imposed RF energy can be determined that will reliably initiate or alter whatever
thermoregulatory response is appropriate to those environmental conditions. For comparison, such determination requires adequate baseline or control data collected under identical conditions. The thermoregulatory profile for the species in question (see below) is useful as a guide to selecting the correct response to measure. The RF intensity so determined can be designated a threshold for response mobilization. However, others (Gordon, et al., 1986) prefer a statistical definition of threshold that is derived from a least squares "hockey stick" analysis (Hasselblad, et al., 1976) of extensive experimental data collected across a wide range of RF intensities at a specific $T_a$. For either method, coherent data are essential for accurate determination of a threshold. By definition, sub-threshold intensities will not produce response alteration or mobilization.

Thermoregulatory profile

During thermoregulation, the particular response that is mobilized, as well as its strength, depends on the prevailing environmental conditions. A schematic "thermoregulatory profile" of a typical endotherm (Figure 2) illustrates how the principal autonomic responses of heat production and heat loss depend on the ambient temperature ($T_a$). The responses shown are steady-state, rather than transient, and the ambient air has minimal movement and water content. Three zones are defined in terms of the prevailing autonomic adjustment. Below the lower critical temperature (LCT), thermoregulation is accomplished by changes in metabolic heat production ($M$), other responses (conductance and evaporative heat loss) remaining at minimal strength. As the $T_a$ falls further and further below the LCT, there is a proportional increase in heat production. At $T_a$ above the LCT, $M$ is generally at a low, resting level that is characteristic of the species, evaporative heat loss is minimal, and thermoregulation is accomplished by changes in thermal conductance. Conductance is a measure of heat flow from the body core to the skin and reflects the vasomotor tone of the peripheral vasculature. As the constricted peripheral vessels begin to dilate, warm blood from the body core is brought to the surface so that the heat may be lost to the environment by radiation, convection, and conduction. These vasomotor adjustments take place within a range of $T_a$ called the thermoneutral zone (TMZ) that is unique to each species. The TNZ for humans is extremely narrow, encompassing only a few degrees around 30 °C. On the other hand, the TNZ for the rhesus monkey extends from 24.5 to 31 °C (Johnson and Elizondo, 1979), that for the squirrel monkey from 26 to 35 °C (Stitt and Hardy, 1971), and that for the mouse from 30 to 33 °C (Hart, 1971). Comparable data for other laboratory animals are provided in the Radiofrequency Radiation Dosimetry Handbook (Durney, et al., 1986).

The upper limit of the TNZ is called the upper critical temperature (UCT). At this $T_a$ the endotherm is fully vasodilated and dry heat loss is maximal. Further increases in $T_a$ stimulate the mobilization of heat loss by evaporation either from the skin (sweating) or the respiratory tract (panting) at a rate that is proportional to the deviation of $T_a$ from neutrality. In humans, whole-body sweating can attain rates of 2 - 3 L/hr and 10 - 15 L/day. Assuming normal hydration, it is difficult for a human to increase $M$ (by exercise) to levels that can not be dissipated by sweating. Since the evaporative heat loss of humans is controlled by both internal and peripheral thermal signals, only an
extraordinarily hostile environment that may include a source of RF energy can be expected to pose a serious threat to a healthy person’s thermoregulatory system. A few reports indicate that nonhuman primates sweat efficiently during RF exposure in thermoneutral and warm environments, while data on RF-exposed rodents are largely equivocal. Human volunteers undergoing controlled RF exposures also sweat efficiently whenever skin and deep body temperatures meet established criteria for the mobilization of this response (Adair, et al, 1998, 1999, 2001a, b; Nadel, et al., 1971).

Many small furred laboratory animals (e.g., mouse, rat, hamster, guinea pig) neither sweat nor pant when exposed to \( T_a \) above the UCT. Any measured increases in respiration rate reflect the general speeding up of all bodily processes as body temperature rises. (This rate increase is often called the "Q-10 effect", which indicates the rate of change of a particular response over a 10 °C change in temperature.) If these species are heat stressed, they must depend on behavioral maneuvers, such as spreading saliva or urine on the fur, or choosing a new environment, to achieve some degree of thermoregulation. Opportunities for behavioral thermoregulation are vital when these species undergo RF exposure, especially in \( T_a \) above the UCT.

As a general rule, RF intensities above an experimentally determined threshold level will also alter the response in question, usually by an amount that is intensity dependent. If the strength of the field is great enough, the response under observation will be altered maximally and the next response in the hierarchy of thermoregulatory responses may be mobilized. This is comparable to moving the endotherm past one of the critical temperatures (i.e., LCT or UCT in Figure 2 in its thermoregulatory profile. A detailed discussion of these concepts and their implication for human thermoregulation during RF exposure is available (Adair, 1987).

Adjustments in metabolic heat production (\( M \))

During acute (a few minutes to a few hours), far-field RF exposure of the whole body, the elevated \( M \) of nonhuman primates (\textit{Macaca mulatta} or \textit{Saimiri sciureus}) is reduced by an amount proportional to the field strength or the SAR (Adair, 1985; 1987; Adair and Adams, 1982; Adair, et al., 1992; Lotz, 1985; Lotz and Saxton, 1987; 1988). As a result of this response adjustment, the internal body temperature is usually regulated with precision within the limits normal for the species. Similar results had been demonstrated earlier in rodents after a period of whole-body irradiation in either a multi-modal cavity or a waveguide. In addition, chronic, low-level RF exposure produces no measurable alteration in the normal metabolism of infant rats (Spiers and Adair, 1987), of rats irradiated throughout their lifetimes (Chou, et al., 1992), or of squirrel monkeys irradiated for 15 weeks (Adair, et al., 1985).

A threshold SAR must be surpassed before a reliable reduction in \( M \) occurs; this threshold is between 0.5 and 1.5 W/kg in nonhuman primates (Adair, et al., 1992; Lotz and Saxton, 1987; 1988) but has not been explored systematically in other species. It should vary with \( T_a \) in accordance with the characteristics of the thermoregulatory profile for each species. Much experimental evidence indicates that both the threshold and the
magnitude of the \( M \) reduction depend, in an orderly way, on the magnitude of the cold stress when the RF field is imposed (Adair, 1985; 1987; Adair and Adams, 1982; Adair, et al., 1992; Lotz and Saxton, 1987; 1988).

During whole-body exposure, the maximal absorption of RF energy occurs when the long axis of the body is parallel to the electric field vector (E-polarization) and the longest dimension of the body is about 0.4 of the free space wavelength (resonant frequency) (Durney, et al., 1986). RF exposure of nonhuman primates at their resonant frequency yields somewhat less efficient thermoregulation than does exposure to sub-resonant or supra-resonant frequencies (Adair, et al., 1992; Krupp, 1983; Lotz, 1985; Lotz and Saxton, 1988). Although the threshold for \( M \) reduction may be lower at resonance (Adair, et al., 1992; Lotz and Saxton, 1988), the magnitude of the response change may be less for a given SAR than at non-resonance and the body temperature may rise. However, the hyperthermia has been found to be modest and well regulated even at SARs equivalent (in W/kg) to the level of resting metabolic heat production in the TNZ.

The situation is similar to that occurring in humans during physical exercise (Adair, 1996). Some have expressed concern that human exposure at resonance may pose a greater hazard than exposure at other frequencies. The studies cited above on non-human primates are reassuring because, even though thermosensors in the skin (necessary for thermal perception and avoidance behavior) may be inefficiently stimulated, there is solid evidence that autonomic mechanisms are rapidly mobilized to dissipate heat generated deep in the body. Experiments recently completed, in which seated human adults undergo 45-min RF exposures at resonance (100 MHz), demonstrate this prediction exactly: no increase in core temperature occurs even at a PD that is 8 time the IEEE C95.1 (1999 edition) standard at this frequency.

If only part of the body is exposed to RF energy, the magnitude of the change in \( M \) reflects the total absorbed energy, as though it were integrated over the whole body (Adair, 1988). If an endotherm is exposed to RF energy at SARs greater than that which reduce \( M \) to the resting level, thermoregulation will be accomplished by mobilization of the next response in the hierarchy, changes in vasomotor state or conductance (Adair, 1985; Candas, et al., 1985; Lotz and Saxton, 1987).

Vasomotor responses

When an endotherm is briefly exposed to RF energy at a \( T_a \) just below the LCT (Figure 2), the stage is set to initiate peripheral vasodilation as soon as \( M \) has been reduced to the resting level. In laboratory animals the vessels of the tail and ears usually vasodilate before those of the extremities. In general, once the RF field strength is sufficient to induce vasodilation (threshold), the response occurs rapidly at field onset and the degree of vasodilation is a direct function of SAR (Lotz and Saxton, 1987; Adair and Adams, 1980; Gordon, et al., 1986) or the total heat load (Gordon, 1983). As \( T_a \) increases above the LCT, the SAR at threshold is reduced (Lotz and Saxton, 1987; Gordon, et al., 1986; Adair, 1985; 1987). Extinction of the RF field results in rapid vasoconstriction. In nonhuman primates, both the threshold and the degree of vasodilation depend on the imposed frequency, although in a species-dependent manner. For rhesus monkeys, the
closer the exposure frequency to whole-body resonance, the less energy is required to
induce vasodilation at a given $T_a$ and the greater the response magnitude at a given SAR
(Lotz and Saxton, 1988). However, for squirrel monkeys exposed to RF energy in cold
$T_a$, higher SARs are required to induce tail vasodilation during exposure at resonance
than at a frequency above resonance (Adair, et al., 1992).

Peripheral vasodilation can also occur spontaneously during the course of a prolonged
RF exposure that is carried out at a $T_a$ below the LCT (Candas, et al., 1985; Lotz and
Saxton, 1987; Adair, 1985; 1987). In this case, vasodilation is mobilized because the
internal body temperature slowly rises during the exposure, eventually surpassing a
threshold for initiation of the response. All of these data support the hypothesis that
vasomotor control is exerted by a combination of central and peripheral thermal neural
signals. In addition, changes in the caliber of blood vessels deep in the body, as well as
in the periphery, accompany RF exposure and the rate of local blood flow increases
dramatically whenever the temperature of the heated tissue exceeds 41 to 42 °C
(Cunningham, 1970). This phenomenon forms one basis for the treatment of localized
malignancies by microwave hyperthermia (Guy and Chou, 1983).

On the other hand, attempts to demonstrate "thresholds" for vasodilation in laboratory
animals held at $T_a$ above the LCT, or at the upper end of the TNZ, do not succeed. Figure
2 shows that partial increases in conductance occur as $T_a$ increases within the TNZ; at the
UCT, by definition, vasodilation is complete. Rapid and significant changes in the local
temperature of the skin in highly vasoactive areas provide a common laboratory index of
peripheral vasodilation in animal subjects. Very low SAR thresholds for an increase in
the temperature of the ear skin have been reported for rabbits held at $T_a$ of 20 or 30 °C
inside a waveguide. Concomitant measures of the SAR threshold for an increase in body
temperature ($T_{co}$) in the same animals were low at $T_a = 20$ °C and virtually indeterminate
at $T_a = 30$ °C (Gordon, et al., 1986). An evaluation of these results with respect to the
thermoregulatory profile for this species reveals certain methodological problems. In
rabbits, the TNZ range is 15 to 25 °C and the upper survival limit is 32 °C (Gonzales, et
al., 1971). Thus, at $T_a = 20$ °C, the animal subjects were already partially vasodilated and
at $T_a = 30$ °C they were fully vasodilated and close to the upper limit of survival. Since
the rabbit pants when heat stressed, a measure of respiratory rate developed for use in
microwave-exposed rodents (Gordon and Long, 1984) could have been used to advantage
in the cited study.

Evaporative adjustments during RF exposure

When the peripheral vasculature of an endotherm is fully vasodilated, dry heat loss
from the body nears its maximum. To prevent significant heat storage and a rise in body
temperature, heat loss by evaporation must be initiated. Figure 2 shows that this occurs
when $T_a = UCT$; it also occurs at $T_a$ within the upper reaches of the TNZ during RF
exposure at SARs sufficiently high to produce full peripheral vasodilation (Adair, 1987).
Because cellular processes in the body speed up as tissue temperature rises, a small
increase in heat production, concomitant with the initiation of evaporation, also occurs at
high $T_a$. Any attempt to predict the evaporative capability of a particular endotherm
during RF exposure must consider the thermoregulatory profile, the avenue of evaporative heat loss available (panting or sweating), or whether such capability may not exist (as is the case with rodents). Fortunately, human beings have an extraordinary capacity to lose body heat by sweating when $T_a$ rises above 30 - 31 °C, or the deep body temperature exceeds 37 °C (Wenger, 1983). Indeed, sweating of human volunteers during RF exposure at high field strengths can be so profuse that core temperature falls significantly (Adair, et al., 2001b).

Sweating from the foot of squirrel monkeys equilibrated to a $T_a$ just below the UCT can be reliably elicited by RF exposure at a threshold SAR equivalent to 20% of the animals' resting $M$ (Adair, 1985). Below this $T_a$, the threshold SAR is linearly related to the exposure $T_a$. Like heat production, the magnitude of the sweating response depends on the integration of absorbed RF energy over the whole body, not energy deposited in some locus such as the "central thermostat" of the hypothalamus. Indeed, thermoregulatory sweating occurs when RF energy is present, even when the hypothalamus is artificially cooled to prevent its temperature from rising (Adair, 1988). During partitional calorimetric studies at cool (20 °C), neutral (26 °C), or warm (32 °C) $T_a$, steady-state tolerance limits were determined for squirrel monkeys, exposed to 2450 MHz CW microwaves, in terms of both power density and SAR (Adair, 1987). The maximal power density tolerated (60 mW/cm²) in a cool environment was equivalent to SAR = 9 W/kg, a value twice the animals' resting $M$. The limiting autonomic response in all cases was sweating, which is not profuse in this species (Stitt and Hardy, 1971). Certain other nonhuman primates (e.g., patas monkey) and, of course, human beings, are far better equipped to dissipate large body heat loads through sweating (Wenger, 1983) than is the squirrel monkey.

Sweating from the calf of rhesus monkeys, during RF exposure at the resonant frequency in thermoneutral $T_a$ of 26 and 32 °C, was reported to occur at somewhat higher SARs, e.g., equivalent to 80% of the animals' resting $M$ (Lotz and Saxton, 1986). In $T_a = 26 °C$, peripheral vasodilation preceded the onset of sweating, as predicted by the thermoregulatory profile. However, sweating in thermoneutral $T_a$, like reduced $M$ in cooler environments (Lotz and Saxton, 1987), failed to prevent a substantial rise in deep body temperature of the rhesus monkey during RF exposure at the resonant frequency.

Researchers agree that careful control over ambient conditions ($T_a$, RH, and $v$) is essential during such exposures to ensure that heat loss from the skin by convection, radiation, and evaporation is not impeded.

Gordon (1982; 1983) reported a much higher threshold (SAR = 29 W/kg) for initiation of evaporative heat loss in microwave-exposed mice. In these studies mice were irradiated inside a closed waveguide and the increase in RH of the air flowing through the waveguide was taken as a measure of heat lost by the evaporation of body fluids. As previously noted, mice neither pant nor sweat but are said to increase respiratory frequency somewhat when heat stressed (Gordon, 1983), in addition to spreading saliva over the fur. None of these responses was observed, nor could the body temperature be recorded during irradiation, to provide evidence that the animals were thermoregulating normally. Since the $T_i$ inside the waveguide was 22 °C, well below the TNZ for the
mouse, changes in $M$ and conductance, not changes in evaporative heat loss, would first be anticipated during RF exposure. Evaporative heat loss should occur only after $M$ was reduced to the resting level and the animal was fully vasodilated. With this perspective, the reported high evaporative threshold for mice may be more easily understood (Adair, et al., 1983; 1984).

Intense or prolonged exposure

Changes in thermoregulatory responses, as a result of exposure to intense RF fields, were explored by Michaelson and his colleagues (Michaelson, 1974). A characteristic triphasic change in internal body temperature accompanied whole-body exposure of dogs to 2880 MHz pulsed microwave fields at an average power density of 1 kW/m² (SAR = 3.7 W/kg) for 6 h or 1.65 kW/m² (SAR = 6.1 W/kg) for 2 - 3 h. The three phases were described as 1) an initial increase in core temperature, 2) a hyperthermic plateau phase, and 3) thermoregulatory collapse. The mobilization of heat loss responses (e.g., panting) was presumably able to counteract the initial effects of RF energy absorption, but only temporarily. The strain on the thermoregulatory system ultimately exhausted the dog's heat loss capabilities and death from hyperpyrexia would follow unless the animal was removed from the field.

Michaelson also found that the $T_a$ at which the exposure occurred was very important (Michaelson, 1983). Dogs could tolerate SARs of 3.7 and 6.1 W/kg at $T_a = 11 \, ^\circ C$ and a SAR of 3.7 W/kg at $T_a = 22 \, ^\circ C$. However, at $T_a = 40.5 \, ^\circ C$, dangerous hyperthermia could occur within 20 min at SAR = 6.1 W/kg. An extended tolerance at high SARs accompanied hydration during the exposure, presumably by affording an increased capacity to lose heat through panting. Another notable finding was the development of tolerance to RF exposure at SAR = 6.1 W/kg as the number of such daily exposures increased. For example, it took only 60 min on the first day, but 220 min on the 34th day, for the dog's core temperature to rise 1.5 °C. This tolerance or adaptation resembles human acclimatization to hot environments (Goldman, 1983).

Candas, et al. (1985) measured changes in physiological thermoregulatory responses of squirrel monkeys exposed to intense 2450 MHz fields in a cold environment ($T_a = 20 \, ^\circ C$) in order to determine if there may be a power density ceiling beyond which further changes in response (e.g., $M$) do not occur. The range of SAR explored was 1.5 to 6.75 W/kg for exposure durations of either 10 or 40 min following a 90-min equilibration to the prevailing $T_a$. They found that during the short exposures a SAR = 5.3 W/kg was required to reduce the elevated $M$ to its resting level within the 10 min. During the long exposures, the resting level of $M$ was achieved within 20 min at a SAR of 4.3 W/kg; at this point, vasodilation of the monkey's tail (the next response in the regulatory hierarchy) usually occurred. The resulting increase in colonic temperature was thereby held to ~1.0 °C.

Walters, et al.(2000) examined whether fatigue during exertional heat stress occurred at a critical internal temperature independent of the initial temperature at the start of exercise. Microwaves (2.1 GHz; 100 mW/cm²) were used to rapidly (3-8 min) heat rats before treadmill exercise to exhaustion. In a repeated-measures design, food-restricted male
Sprague-Dawley rats (n = 11) were preheated to three levels (low, medium, and high). In addition, two sham exposures, Sham 1 and Sham 2, were administered at the beginning and end of the study, respectively. At the initiation of exercise, hypothalamic (T$_{hyp}$) and rectal (T$_{re}$) temperatures ranged from 39.0 °C to 42.8 °C (T$_{hyp}$) and 42.1 °C (T$_{re}$). The treadmill speed was 17 m/min (8 degrees grade), and the ambient temperature during exercise was 35 °C. Each treatment was separated by 3 wk. Run time to exhaustion was significantly reduced after preheating. There was a significant negative correlation between run time and initial T$_{hyp}$ and T$_{re}$ ($r = 0.73$ and 0.74, respectively). The temperatures at exhaustion were not significantly different across treatments, with a range of 41.9-42.2 °C (T$_{hyp}$) and 42.2-42.5 °C (T$_{re}$). There were no significant differences in run time in the sham runs administered at the start and end of the investigation. No rats died as a result of exposure to any of the treatments, and body weight the day after each treatment was unaffected. These results support the concept that a critical temperature exists that limits exercise in the heat. This temperature is very close to that determined by Cunningham (1970) as the threshold for a significant increase in blood flow that helps prevent severe heat stress in humans.

The potential for high intensity millimeter wave exposure to produce lethality in the anesthetized laboratory rat has recently been explored (Frei, et al., 1995; Ryan, et al., 1996). Exposure at millimeter wave frequencies deposits RF energy on the skin surface of the animal's body, stimulates rapid peripheral vasodilation and decreased vascular resistance in the body core, and ultimately reduces arterial blood pressure with eventual circulatory collapse and death. These symptoms resemble heat shock, except that the core body temperature increases only a few degrees above the normal level. For example, exposure of anesthetized rats to 35 GHz at a power density of 75 mW/cm$^2$ (SAR = 13 W/kg) produced a rapid rise in local (irradiated) skin temperature (from 36 to 48 °C), increased heart rate, mesenteric vasodilation, circulatory collapse, and death, even though the colonic temperature had reached only 40.3 °C. Additional studies of this phenomenon (Ryan, et al., 1996, 1997) have concluded that neither age nor excess levels of nitric oxide contribute to the hypotensive state that results from millimeter wave exposure of the anesthetized rat at high field strengths. Jauchem and Frei (1992) have provided a comprehensive review of the cardiovascular (heart rate and blood pressure) changes that result from excessive RF exposure vs environmental heating and that may contribute to lethality. They concluded that altered core-to-skin thermal gradients, especially during RF exposure, may play an important role in the enhanced potential for cardiovascular impairment.

Exposure of endothermic organisms, including humans, to new electromagnetic energy sources that feature very high peak power, nanosecond pulses composed of an ultra-wideband (UWB) of frequencies may pose potential health risks that require evaluation. A paper by Walters, et al. (1995) reported the results of single 2-min exposures of rats to UWB (60 Hz pulse frequency, 5-10 ns pulse width, 0.25 - 2.5 GHz bandwidth) on a broad range of physiological and behavioral variables that could indicate potential hazard. Following the acute exposure, each of 32 animals was examined on one of the following tests: 1) a functional observational battery (Moser, et al., 1991), 2) a swimming performance test, 3) a complete panel of blood chemistries, and 4) a determination of the
c-fos protein in immunohistologically-stained sections of the brain. In addition, colonic
temperature of each rat was determined immediately before and after both sham and
UWB exposure. No significant differences were found on any of the measured
dependent variables between sham and UWB-exposed animals.

Effects of RF exposure on early development

A few studies have examined the potential for changes in physiological responses to RF
exposure during early development, either in utero or in the early post-natal period. Most
of these have used laboratory rats as subjects and the principal endpoints have been
related to growth and development. Only those studies that concern changes in some
thermoregulatory responses are discussed here.

The young rat's ability to maintain a constant body temperature improves under normal
conditions during the first 3 weeks after birth (Spiers and Adair, 1986; Conklin and
Heggeness, 1971; Takano, et al., 1979). It is possible that the immature rat might be
capable of responding effectively to a rapid internal deposition of RF energy. Guillet and
Michaelson (1977) reported that 5-min exposure of the neonatal rat to 40 mW/cm²
produced a 1.5 to 2.5 °C rise in deep body temperature (T\text{b}) measured rectally. Spiers, et
al.(1989) have shown that, at 6 - 7 days of age, there was a 1.7 °C increase in the T\text{b} of
neonatal rats at T\text{a} = 25 °C at the end of a 60-min exposure to 2450 MHz (5 mW/cm²,
SAR = 3 W/kg), but no change in metabolism (M). Exposure to 20 mW/cm² (SAR = 12
W/kg) for 60 min produced a 3.4 °C increase in T\text{b}. In contrast to the 5 mW/cm²
exposure, there was a progressive reduction in M (7.2 W/kg at 60 min exposure), which
began only after T\text{b} rose above 34.7 °C.

Few studies have determined if repeated RF exposure of the young mammal alters
growth and physiological development. Michaelson, et al. (1978) had reported that a 1 h
exposure to 2450 MHz CW microwaves at 10 - 40 mW/cm², during days 0 - 2 of
gestation produced offspring that might show a greater metabolic response to cold T\text{a} than
was found in sham exposed dams. Spiers and Adair (1987) reported that repeated
exposure (4 h/day for 10 days) of the young rat (6 - 17 days of age) to 5 mW/cm² (SAR =
1.8 - 2.7 W/kg) did not alter growth rate in cold T\text{a} or result in significant post-treatment
shifts in thermoregulatory ability. Galvin, et al. (1986) reported that rats exposed
prenatally (3 h/day for days 5 - 20 of gestation) to 2450 MHz microwaves (10 mW/cm²,
SAR - 2 - 4 W/kg) weighed more than sham-exposed animals at 30 days of age.

Another study examined the thermal and metabolic responsiveness of Japanese quail
embryos following repeated exposure of the egg to 2450 MHz microwaves and the
potential for microwave incubation as an alternative to conventional heating (Spiers and
Baummer, 1991). Eggs were exposed (8 h/day) for days 1 - 15 of incubation at 5 or 20
mW/cm² in 3 T\text{a} (30.0, 33.1, or 35.4 °C). The SAR for 15-day old incubated eggs was
0.66 (W/kg)/(mW/cm²). Other eggs were concurrently sham exposed at each of 5 T\text{a} from
27.9 to 37.5 °C. Eggs were tested on day 16 of incubation (RF absent) to measure
embryo M and internal and external egg temperature at different T\text{a}. Repeated RF
exposures, at T\text{a} = 30 °C, to 5 and 20 mW/cm² increased wet embryo mass on day 16 by 9
and 16% respectively compared to predicted values for unexposed eggs at the same $T_a$

No differences in either $M$ or total heat transfer to the environment were found between sham- and RF-exposed eggs, leading to the conclusion that repeated RF exposures did not result in altered physiological development. Thus, RF irradiation can be used to increase egg temperature and embryonic growth rate at $T_a$ below normal incubation level without altering the basic metabolic and thermal characteristics of the developing bird.

**Thermal hot spots**

Thermographic studies on tissue-equivalent models of humans and animals (Guy, 1971; Guy, et al., 1974) have indicated regions of high local SAR during exposure of the whole body to plane wave RF fields. Wrists, ankles, and neck (also the base of animal tails) are predicted to be foci of enhanced energy absorption where excessive elevations of tissue temperature may occur. Krupp (1983) studied anesthetized rhesus monkeys, equilibrated to $T_a = 23^\circ C$ and exposed for 1 - 4 hours to planewave 210 MHz RF energy (PD = 5 - 27 mW/cm²). The data showed substantial increases in core temperature but no evidence for localized regions of greatly elevated temperature (i.e., tissue "hot spots") in wrist, ankle, thigh, or biceps. Similar experiments at 2.06 GHz (Krupp, 1981) employed the same techniques for temperature measurement and exposure of rhesus monkeys but different results were found. At PD = 15 mW/cm², 1 hour of RF exposure produced no increase in rectal temperature or localized temperatures measured in neck and groin. Wrist and ankle temperatures rose slowly over the 1-hr exposure but never reached the rectal temperature value. Krupp concluded that increased convective heat transfer by the blood during such exposures, coupled with lower set point temperatures in the limbs, could protect individual tissues from overheating.

**Circadian variations**

It is essential that quantitative studies of thermoregulatory function always be conducted at the same time of day, because a circadian rhythm of regulated changes in body temperature is characteristic of all endotherms. Lotz (1983) showed the influence of this circadian rhythm on the elevation of rectal temperature in rhesus monkeys exposed or sham exposed to 1.29 GHz pulsed energy at a whole-body SAR of 4.1 W/kg. The exposure duration of 8 hours occurred either during the day or during the night. The change in deep body temperature resulting from these exposures was nearly identical (~1.6 °C), but the peak temperature was about 1.0 °C lower at night, a value equal to the normal nocturnal fall in body temperature of this species. Plasma cortisol was also monitored during the experiments and was elevated only during the daytime exposures. Lotz suggested that this response may depend simply on the absolute level of body temperature rather than the magnitude of temperature change during RF exposure.

**Chronic exposure studies**

Of the several studies in which groups of animals have been exposed to RF fields for many months or even years, only three to date have evaluated the consequences for
thermoregulation to any extent. Guy, et al. (1980) exposed male New Zealand white rabbits to 2450 MHz CW microwaves at 10 mW/cm², 23 h/day for 180 days. Eight rabbits were studied simultaneously, 4 irradiated and 4 controls. Each animal was housed in a miniature anechoic chamber at $T_a = 24 \pm 2 ^\circ C$; the chamber contained a drip watering system and a food hopper. The exposed animals were irradiated from a horn located in the ceiling of the chamber. Thermographic measurements indicated a peak SAR of 17 W/kg in the head while whole-body SAR was estimated at 1.5 W/kg (Durney, et al., 1986). Periodic assessments of the animals revealed no significant differences between the groups in body mass, urinary output, body temperature, hematocrit, hemoglobin, or basic blood cell counts.

Adair, et al. (1985) studied the changes in thermoregulatory behavior and autonomic thermoregulatory mechanisms in pairs of squirrel monkeys chronically exposed (or sham exposed) 40 h/week for 15 weeks to 2450 MHz CW RF energy at 2 power densities (1 and 5 mW/cm²) in each of 3 $T_a$ (25, 30, or 35 °C). The whole-body SAR, as measured in phantom models filled with muscle-equivalent material, was 0.16 (W/kg)/(mW/cm²). Standardized tests of autonomic thermoregulatory responses were conducted several times 1) during a pre-exposure phase of 8 to 12 weeks; 2) during the 15-week chronic exposure period; and 3) during a post-exposure phase of 4 to 8 weeks. During the tests, the following variables were measured at several controlled $T_a$: colonic temperature, 4 representative skin temperatures, oxygen consumption, and sweating rate from the foot. In addition, blood samples were taken at 1, 5, 10, 15, and 20 weeks of the treatment for analysis of cell counts, hemoglobin, serum thyroxin, thyroxin binding capacity, blood sodium, potassium, bicarbonate, chloride concentrations, total serum protein, and albumin. The results of the tests showed no significant differences in metabolic heat production, internal body temperature, or blood indices between sham and exposed animals. However, the $T_a$ prevailing during the exposure did exert an effect on sweating rate, which was enhanced in $T_a = 35 ^\circ C$, an effect of acclimatization to heat. Skin temperature was found to be reliably influenced by both $T_a$ and RF exposure. The most robust effect was a reduction in body mass in the exposed animals that was directly related to power density.

Chou, et al. (1992) studied the effects of chronic exposure of 100 sham-exposed rats and 100 rats exposed throughout their lifetimes to circularly-polarized 2450 MHz pulsed (10 µsec duration, 800 pps) RF energy (Guy, et al., 1979). The only variables among the 155 measured that relate directly to this review are $O_2$ consumption and $CO_2$ production. These were assessed in a subsample of 18 rats from each group. A significant decrease in both $O_2$ consumption and $CO_2$ production was seen in the exposed young animals but not in the exposed mature animals.

Pulsed vs CW field effects

Few systematic investigations of the biological effects of pulsed vs CW fields have been undertaken and almost none have related to the thermoregulatory responses of the exposed biological target. The most extensive investigation of pulsed field effects, apart from studies of the "microwave hearing" phenomenon or recent reports of high peak power microwave exposure (D'Andrea, et al., 1989), have been a product of the pulsed
circular waveguide exposure system developed by Guy and colleagues (1979). Many papers published by Lai and his co-workers (e.g., Lai, et al., 1984a,b) have described complex interactions between 2450 MHz pulsed microwave exposure of rats in circular waveguides and drugs that influence the body temperature. However, all conclusions are related to periodic measurements of colonic temperature alone; no data on the specific autonomic mechanisms that may underlie changes in that temperature are provided.

Historically, it has been held that pulsed radiation is more likely to produce certain biological effects than in CW radiation at the same average incident power density and, indeed, the results of several experiments have supported this view. A recent evaluation (Postow and Swicord, 1996) has elaborated on this possibility. "Although the total amount of energy delivered to the absorber is the same for CW and pulsed irradiation at the same frequency and with the same time-averaged power, the time course of energy deposition and dissipation is different. Depending on the pulse parameters and the size, shape, thermal environment, etc. of the absorbing material, this difference may be significant and may alter physiological responses in a way that depends on the conditions of pulse modulation." (op.cit., p. 563).

Few studies have examined the comparative effects of exposure to pulsed and CW fields on the autonomic responses of intact animals. In general, the effects on heart rate have been equivocal. One study (Frei, et al., 1988) found a significant increase in the heart rate of anesthetized rats in the presence of high intensity pulsed 2.8 GHz fields. However, these authors later reported no difference between thermogenic CW and pulsed fields at 2.8 and 9.3 GHz on heart rate, respiration rate, blood pressure, and ECG (Frei, et al., 1989a, b). The reason for the difference in findings is unclear. Others (Lu, et al., 1992) have found no difference in heart rate and blood pressure changes produced by equivalent CW and pulsed fields.

A series of experiments assessed the thermoregulatory consequences of 90-min RF exposure of squirrel monkeys under several exposure parameters (Adair, et al., 1993). Specific parameters investigated were frequency (450 and 2450 MHz), exposure mode (CW and pulsed fields), whole-body SAR (range = 1.2 - 4.7 W/kg) and the prevailing $T_a$ (20, 26, and 32 °C). The pulse parameters studied were 20 µsec pulse width, $2.5 \times 10^4$ pps. Groups of four monkeys (three sessions each) were tested under each exposure condition. In general, the steady-state thermoregulatory responses (colonic and skin temperatures, metabolic heat production, conductance, and sweating rate) to pulsed and CW fields were found to be the same at a given frequency, $T_{as}$ and whole-body SAR. These studies laid the groundwork for the four studies of human volunteers reported earlier in this review (Adair, et al., 1998, 1999; 2001a,b).

Additive drug-microwave interactions, including anesthetics

More than 20 years ago, it was recognized that experimental animals treated with certain drugs were especially vulnerable in the presence of RF fields. Michaelson and his colleagues (1974) reported that dogs show a greater susceptibility to microwave heating after administration of pentobarbital sodium, morphine sulfate, or chlorpromazine,
suggesting that mechanisms of heat loss may be compromised by the drug treatment. A similar effect was demonstrated in rats rendered hypothermic by cortisone injections; animals so treated sustained greater increases in core temperature than did non-treated control animals during RF exposure at 40 W/kg (Putthof, et al., 1977). In rabbits and rats, increased vulnerability was also shown to take the form of a delayed rise in deep body temperature, reflecting the hypothermic action of the anesthetic (Michaelson, 1974). On the other hand, the duration of hexobarbital anesthesia in mice (Blackwell, 1980) and pentobarbital anesthesia in rabbits (Cleary and Wangemann, 1975) were found to be related directly to the field strength of a 2450 MHz exposure. This shortening of anesthesia apparently results from a higher rate of distribution of the drug through increased blood flow, a thermoregulatory response. Other archival studies have reported an increased survival of rodents, treated with general anesthetics prior to RF exposure at high power densities.

The picture is further complicated by other factors. Lai, et al. (1984b) reported that both the orientation of the animal during exposure and the order of presentation of anesthetic and microwaves can influence the magnitude and duration of anesthesia. In these studies, rats were exposed for 45 min to 2450 MHz circularly polarized, pulsed microwaves (2µsec pulse, 500 pps) at SAR = 0.6 W/kg. When microwave exposure preceded injection of the anesthetic, recovery from hypothermia was lengthened. When anesthesia preceded irradiation, posterior-exposed animals recovered from anesthesia significantly faster than anterior- or sham-exposed animals. Polarization was shown to be important. When ketamine-anesthetized rats were exposed to 1.23 GHz CW microwaves at SAR = 8 W/kg, E-polarization generated greater tissue heating (colonic, tympanic, subcutaneous and tail surface temperatures) than H-polarization (Jauchem, et al., 1990). Similar results were found for 2.45 GHz, although tissue heating was more superficial at this higher frequency (Frei, et al., 1989b).

Synergistic effects of psychotropic drugs and ethanol

Chlorpromazine, a psychotropic drug, has been widely investigated for possible synergistic action with RF exposure (Jauchem, 1985). Early studies indicated a greater susceptibility to tissue heating and a decreased survival time in unanesthetized animals that had been treated with chlorpromazine prior to high power RF exposure. More recent studies (Jauchem, et al., 1985; 1988) have featured microwave irradiation of anesthetized rats injected with either saline or chlorpromazine (5 mg/kg) and held at $T_a = 24$ °C. Two RF conditions were studied: 2.8 GHz PW (2 µsec pulse, 500 pps) at SAR = 14 W/kg and 5.6 GHz CW at SAR = 12 W/kg. Under both exposure conditions, chlorpromazine tended to enhance thermoregulatory efficiency when the rat's colonic temperature was not allowed to rise above 39.5 °C, but the drug increased susceptibility to RF when the exposure was continued until death from hyperpyrexia occurred. Other psychotropic drugs of similar nature, amitryptaline HCl (10 mg/kg) and haloperidol (0.1 mg/kg) were not found to alter the thermal responses of anesthetized rats to 2.8 GHz PW exposure at SAR = 14 W/kg. While these studies are important, they have limited generality because ranges of SAR, drug dose, and $T_a$ have yet to be explored.
The importance of conducting parametric studies becomes clearer when scientists explore the potential synergy between RF exposure and other substances whose physiological action tends to alter the body temperature. Ethanol is a classic example. We know that the magnitude of ethanol-induced hypothermia in the rat is highly dependent on both the dose administered and the \( T_a \) to which the animal is exposed. One can even observe hyperthermia in ethanol-treated rats if the prevailing \( T_a \) is well above thermoneutrality (e.g., 36 °C), a response that Myers (1981) has interpreted to reflect the alteration of heat loss mechanisms. However, careful parametric studies (Spiers, et al., 1984) have demonstrated, for \( T_a \) from 17 to 32 °C, that acute administration of ethanol at a commonly-used dose of 3 g/kg interferes with metabolic heat production rather than with heat loss. A more important finding was that rats, equilibrated to \( T_a = 26 \) °C prior to ethanol dosing and testing at \( T_a = 17 \) °C, showed an initial metabolic depression that slowed the developing hypothermia.

This kind of information is essential to the proper interpretation of measured changes in colonic temperature in ethanol-treated rats that had previously been either sham exposed or irradiated for 45 min by 2.45 GHz, circularly polarized, pulsed microwaves (2 µsec pulse, 500 ps) at SAR = 0.6 W/kg (Lai, et al., 1984a). In this study, the mean \( T_a \) was 22 ± 0.1 °C, but the range was 21 - 24 °C. All rats were injected IP with ethanol at 3 g/kg. No control injections of the vehicle were given. Of greater importance, since no dependent variable other than colonic temperature was measured, it was impossible to determine whether alterations in heat production or heat loss contributed to the observed attenuation of hypothermia in the RF-exposed animals relative to the sham exposed. Lai, et al. reported that microwave exposure alone produced no change in colonic temperature. However, abundant evidence exists for the maintenance of normothermia (constant deep body temperature) during RF exposure, even at moderately high SARs (Adair, 1987; Candas, et al., 1985; Lotz and Saxton, 1988). The underlying cause is careful titration of heat production and/or heat loss. Thus, the speculation by Lai, et al. (1984a) that their results might reflect stress-related interference with heat loss, perhaps mediated by endogenous opioids, is open to question. It seems clear that a complete understanding of the subtle actions of RF exposure requires measurements of many more responses than simply the changes in "colonic temperature" taken at arbitrary intervals in experimental subjects.

Rodent data in circular waveguide

Lai and his colleagues undertook an extensive research program to determine how endogenous opioids may be involved in the interaction between certain psychoactive drugs they injected in rats and prior acute irradiation by circularly-polarized 2.45 GHz pulsed microwaves at SAR = 0.6 W/kg (Lai, et al., 1987). The early hypothesis-generating experiments usually followed the same protocol: a 45-min sham or microwave exposure in a circular waveguide was followed by 1) colonic temperature measurement, 2) injection of a drug at a single dose, and 3) measurement of colonic temperature every 15 min for periods ranging from 45 min to 2 hr. Most studies suffered from the limitations noted above, including a narrow range of \( T_a \), a single drug dose, infrequent assessment of the effects of vehicle injection, and no tests for specific contributing
thermoregulatory mechanisms. Apomorphine-induced hypothermia was reported to be enhanced by RF exposure while amphetamine-induced hyperthermia was attenuated (Lai, et al., 1984b). A more extensive study determined that injection of 1 or 2 ml/kg of distilled water produced a greater post-irradiation hyperthermia in RF exposed animals than in those sham exposed. This hyperthermia was attenuated by injections of naltrexone, a narcotic antagonist, or one of the serotonin antagonists: cinanserin, cyproheptadine, or metergoline (Lai, et al., 1984c). But the hyperthermia was not altered by the peripheral serotonin antagonist xylamidine or the dopamine antagonist haloperidol.

The previously reported (Lai, et al., 1984b) attenuation (by prior RF exposure) of amphetamine-induced hyperthermia was found, in a separate experiment, to depend on the dose of morphine (1, 5, 10, 15, and 20 mg/kg SC) injected before the amphetamine dose (5 mg/kg IP). The authors reported that amphetamine-induced hyperthermia, attenuated by low level pulsed microwaves, could also be classically conditioned by repeated (10 days) microwave exposures prior to the attenuation test. Sensory cues in the waveguide, adaptation to stress produced by microwave exposure, and involvement of endogenous opioids were all considered as mediators in these effects. Direct thermal effects on metabolic heat production, thermal conductance, and convective or evaporative heat loss are also prime candidates for investigation under these conditions.

Rodent data in far field

Smialowicz (1983) used drug-microwave interactions to demonstrate subtle heating produced by low-intensity (= 10 mW/cm²) exposure to 2.45 GHz CW microwaves in both mice and rats. Mice injected IP with 5-HT creatinine sulphate complex (20 mg/kg) and rats injected IV with Salmonella typhimurium LPS (100 µg/kg) became hypothermic when held at $T_a = 22^\circ$C. Post-injection exposure to RF energy generated an increased colonic temperature that was a direct function of the power density of the imposed field. Saline-injected control animals, similarly exposed, did not show comparable elevations of core temperature. Thus, the study demonstrated that chemical impairment of thermoregulatory mechanisms could permit detection of significant changes in the body temperature of experimental animals exposed to low-intensity RF fields that were formerly believed to be non-thermogenic.

Primate studies

Many other classes of drugs interact with RF exposure to alter body temperature in interesting ways. One study (Adair, 1987) examined the potential for disruption of autonomic thermoregulatory responses by an altered metabolic state (induced by injections of isoproterenol) in squirrel monkeys exposed to 2.45 GHz CW microwaves at thermoneutrality ($T_a = 33^\circ$C). Unlike shivering thermogenesis, chemically-mediated nonshivering thermogenesis was unaffected by RF exposures at whole-body SARs from 1.5 to 4.0 W/kg. Instead, the elevated energy production/absorption in the body, coupled with partially disabled heat loss responses, produced an exaggerated rise in internal body temperature. These results confirm and extend a conclusion drawn by others that an endotherm whose thermoregulatory system is compromised by drugs or other agents may
be at a disadvantage, in terms of its ability to regulate the body temperature, during exposure to RF fields.

**Thermoregulatory behavior in the presence of RF energy**

Any organism may adopt thermoregulatory behavior as an alternate strategy to counter the thermalizing effects of RF exposure. Changes in certain behaviors can alter the thermal characteristics of the air/skin interface and maximize the efficiency of heat transfer to the environment. Examples are the selection of a more favorable thermal environment, the resetting of a thermostat, and the putting on or taking off of clothing (insulation). These behaviors also minimize the involvement of autonomic mechanisms of heat production and heat loss, conserve bodily stores of energy and fluid, and generate a state of maximal thermal comfort. Because behavioral responses may be mobilized quickly and are of high gain, they must always be considered in any discussion of the thermoregulatory consequences of RF exposure. A discussion of the behavioral responses that contribute to thermoregulation in the presence of RF fields may be found in a separate white paper.
REFERENCES


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