

Radiofrequency (RF) Effects on Blood Cells, Cardiac, Endocrine, and Immunological Functions

David R. Black^{1*} and Louis N. Heynick²

¹*Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*

²*Independent Consultant, Palo Alto, California*

Effects of radiofrequency electromagnetic fields (RFEMF) on the pituitary adrenocortical (ACTH), growth (GH), and thyroid (TSH) hormones have been extensively studied, and there is coherent research on reproductive hormones (FSH and LH). Those effects which have been identified are clearly caused by heating. The exposure thresholds for these effects in living mammals, including primates, have been established. There is limited evidence that indicates no interaction between RFEMF and the pineal gland or an effect on prolactin from the pituitary gland. Studies of RFEMF exposed blood cells have shown that changes or damage do not occur unless the cells are heated. White cells (leukocytes) are much more sensitive than red cells (erythrocytes) but white cell effects remain consistent with normal physiological responses to systemic temperature fluctuation. Lifetime studies of RFEMF exposed animals show no cumulative adverse effects in their endocrine, hematological, or immune systems. Cardiovascular tissue is not directly affected adversely in the absence of significant RFEMF heating or electric currents. The regulation of blood pressure is not influenced by ultra high frequency (UHF) RFEMF at levels commonly encountered in the use of mobile communication devices. Bioelectromagnetics Supplement 6:S187–S195, 2003. © 2003 Wiley-Liss, Inc.

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INTRODUCTION

This study has its origins in collation of *in vivo* effects in those documents found suitable for use in revising or reaffirming the IEEE [1991] standard for maximum permissible exposure of humans to radiofrequency electromagnetic fields (RFEMF) by the IEEE International Committee on Electromagnetic Safety (ICES) Subcommittee 4 (SC4). Reference has been extended to *in vitro* research work where necessary.

Physiological regulatory systems provide humans and other warm blooded species with accurate and interdependent homeostatic systems that maintain body temperature and also regulate immune and neuroendocrine functions. One of the functions of these systems is to sensitively monitor both environmental and internally generated energy, although they may not have the ability to distinguish between the sources. There is substantial literature documenting the homeostatic responses of various species to RFEMF exposure. Taken as a whole, the findings are generally consistent, and those effects that have been established are difficult to separate from those of other nonspecific stressors, particularly heat.

Much of the early work that sought possible effects of RFEMF on blood cells exposed *in vitro* suffered from a lack of adequate control of cell temperature during exposure. In later studies using effective temperature control, nonsignificant differences were obtained with exposed cultures held at the same temperature as control cultures for the same durations. In studies where temperature elevation of culture by RFEMF or conventional means did show adverse effects, these were clearly of thermal origin [Roberts et al., 1986].

There is substantial, evidence based consensus that neuroendocrine effects from RFEMF only occur at

*Correspondence to: Dr. David R. Black, Occupational Medicine Unit, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand.
E-mail: d.black@auckland.ac.nz

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levels greater than specific exposure thresholds [Lotz and Podgorski, 1982]. Whilst these thresholds are somewhat variable, both in terms of species and environment, the range of observed responses documented in research on mammals has provided biological endpoints and threshold levels that now serve as criteria for hazard evaluation and therefore are useful in standards setting. The research into cardiovascular effects of RFEMF suggests that neither whole body exposure nor localized exposure of cardiac tissue causes cardiovascular effects below levels at which heating is expected to occur, unless biologically significant electric currents are directly involved [WHO, 1993].

ENDOCRINE FUNCTION—PITUITARY GLAND AND ITS AXES

The anterior pituitary gland, or adeno-hypophysis, is a classical gland containing cells that secrete chemical messengers in the form of hormones. Very small quantities of hypothalamic hormones are transported without dilution directly to their target cells in the anterior pituitary. The chain of control from the hypothalamus through the hormonal system and back via the negative feedback mechanism are known as axes, each of which is a notional circuit of neurochemical control [Wilson, 1994].

Radiofrequency (RF) Field Effects on the Pituitary Axes: Corticosteroid

Adrenocorticotrophic hormone acts on the cortex of the adrenal gland and stimulates the secretion of steroid hormones. Endocrine responses can be an adaptive response to environmental stimuli that are not necessarily adverse, analogous to a febrile response when there is a need for host immune defense. There is reliable evidence that plasma steroid levels in rats are significantly increased by exposure to RFEMF above certain levels for which thresholds have been reasonably accurately determined.

By 1978 it had become clear that the observed stimulation of the adrenal axis in RFEMF exposed experimental rats was usually a systemic process resulting from general hyperthermia. Adrenocortical stimulation is generally accepted as indicating a physiological response to a stressful stimulus; however, exposure of rats to RFEMF at an SAR of 5 W/kg was consistently found to stimulate the Hypothalamic-Hypophysial-Adrenocortical (HHA) axis, and this was modulated by the central nervous system (CNS) [Lotz and Michaelson, 1978]. Responses below 5 W/kg are variable, and observations are confounded by normal physiological variations in these hormone levels.

Increases observed in adrenal function due to RFEMF exposure is consistently correlated with rises of colonic temperature in rats. Plasma corticosteroid levels in hypophysectomised rats exposed to less than 12 W/kg were below control. When normal animals were treated with Dexamethasone, a potent corticosteroid that switches on the negative feedback before exposure, the cortical response was suppressed. It was concluded that these results suggest that RFEMF exposure induced CNS response observed in intact rats is dependent on adrenocorticotrophic hormones secreted by the pituitary [Lotz and Michaelson, 1978, 1979]. Therefore, the adrenal gland is not the primary endocrine gland stimulated by RFEMF exposure.

The evidence from these experiments was consistent with the existing hypothesis that stimulation of the adrenal axes in rats exposed to RFEMF is a systemic process due to general hyperthermia to which the pituitary is known to respond [Lu et al., 1981]. Later research found an increase in serum cortisol levels and increased rectal temperature in monkeys exposed to 1.29 GHz RFEMF at 3–4 W/kg for 4 h, but there was no change in serum growth hormone levels or thyroxin. When the SAR was increased to 4.1 W/kg and exposure time lengthened to 8 h, increased serum corticosteroid levels were seen during the day, but no change was observed when the animals were exposed at night with a commensurate rise in rectal temperature [Lotz and Podgorski, 1982].

A similar experiment with rats exposed to 255 MHz CW RFEMF for 4 h at an estimated SAR of 3–4 W/kg showed no change in serum cortisol level, but a rectal temperature increase of 1.5–2 °C [Lotz, 1985]. It is therefore concluded that plasma corticosteroid levels in rats are significantly enhanced by exposure above a definite threshold level with increasing duration of exposure, and that similar effects are found in the corticosteroid response in primates. This response seems to vary in amplitude related to the circadian rhythm of corticosteroid levels. The boundary between an effect and no effect appears to be of the order of 4 W/kg in these mammalian species [Lotz, 1983].

Growth and Thyroid Hormones

Growth hormone acts on liver and adipose tissue (fat) and indirectly promotes growth, and controls protein, lipid, and carbohydrate metabolism. Michaelson et al. [1975] reported decreases in serum growth hormone levels in young rats exposed for more than 60 min to 2.45 GHz CW RFEMF at SAR levels estimated to be up to 7.5 W/kg. Lu et al. [1980] found that the threshold for induction of changes in serum growth hormone level depended on the baseline of growth hormone level in the experimental animals at the time of

exposure; however, there was no change in thyroxine levels and no effect with exposure to 2.45 GHz RFEMF at 10.5 W/kg for 1 h or at 0.2 W/kg for 2 h.

Thyroid stimulating hormone (TSH) acts on the thyroid gland and stimulates secretion of thyroid hormones. Magin et al. [1977] reported increased thyroxine (T_4) and triiodothyronine (T_3) secretion when the thyroids of dogs were exposed to varying levels of 2.45 GHz RFEMF at estimated SARs of 58–190 W/kg for 2 h. A followup study [Lu et al., 1980] found decreased circulating thyroxine and TSH levels in rats when a rectal temperature rise to 40 °C had been caused by whole body exposure to 2.45 GHz CW RFEMF at 4 W/kg. The research previously referenced [Lotz and Podgorski, 1982] using rhesus monkeys, which found an increase in serum cortisol levels with increased rectal temperature when exposed to 1.29 GHz RFEMF at 3–4 W/kg, did not report a change in serum growth hormone levels or thyroxin.

As most recently described by Chou et al. [1992], Guy and coworkers at the University of Washington undertook a lifetime study of rats exposed to 2.45 GHz RFEMF at a whole body SAR between 0.15 and 0.4 W/kg. The rats were exposed from 2 to 27 months of age. No differences were reported in plasma endocrine levels between exposed and sham exposed animals.

Prolactin is a complex hormone consisting of 198 amino acids with molecular weights between 23 000 and 100 000. It is essential for lactation, during which the lactotrophs form 70% of the pituitary. There are receptors in the breast and gonads. Prolactin is a promoter for breast cancer in rodents, but there is no proven analogy in humans. Toler et al. [1988] investigated the effects of long term, low level exposure to 435 MHz RFEMF on various physiological systems in a large rodent population. Chronic exposure to the low level pulsed RFEMF field resulted in no adverse effects on animal health, as measured by the range of blood borne endpoints, which included prolactin levels.

Pineal Gland

An effect of RFEMF on the production of melatonin by the pineal gland has been suggested, but never reliably established. The pineal is involved in the regulation of circadian rhythm and is affected by light, but this is likely to be on the basis of retinal sensitivity, although not necessarily in the rods or cones [Thapan et al., 2001]. An ecological animal study [Stark et al., 1997] argues against an effect at low levels, while a recent human experimental study suggests there is no effect at cellular telephone handset levels [de Seze et al., 1998]. However, there is continued interest in the possible role of both prolactin and melatonin in human breast cancer. A study from Norway has suggested an

association between breast cancers in women aged 50 years and older with shift work. In comparison with all Norwegian women born in 1935 or later, the relative risk was 1.5 after adjustment for fertility factors [Tynes et al., 1996].

Renal Hormones

Angiotensins, hormones formed in the blood that have effects on renal tissue, are important in the regulation of blood pressure. The most important group of modern antihypertensive drugs, angiotensin converting enzyme (ACE) inhibitors, acts on the angiotensin mechanism. Any such effect could be clinically important but has not yet been studied. However, studies of possible effects of RFEMF exposure on blood pressure do not show any relationship [Braune et al., 1998, 2002].

Gonadotrophic Hormones

The gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) are glycoproteins secreted by the gonadotrophs, which make up about 10% of the anterior pituitary. Wilson [1994] and Mikolajczyk [1978] found an increase in LH but no change in FSH levels in rats from exposure to 2.8 GHz RFEMF at 100 W/m² for 6 h a day, 6 days a week, for 6 weeks.

Lifetime Studies

In the previously discussed chronic exposure study by Guy and coworkers at the University of Washington, one group of 100 male rats was exposed unrestrained to 2.45 GHz RFEMF at average power density about 0.48 mW/cm² in individual cylindrical waveguides under controlled environmental and specific pathogen free conditions. Another group of 100 male rats was similarly sham exposed. Exposures were begun at age 8 weeks and continued for 25 months (whole body SAR, 0.15–0.4 W/kg). One of the endpoints investigated was whether such exposures would affect the immune system of the rats.

There were no overall significant differences between RFEMF exposed and sham exposed rats in the hematologic parameters. Differences in thyroxine (T_4) levels between the RFEMF exposed and sham exposed rats were nonsignificant, indicating that the RFEMF had no effect on the hypothalamic pituitary thyroid feedback mechanism. As expected, however, the T_4 levels of both groups decreased significantly with age.

Toler et al. [1988] implanted cannulas in the aortas of 200 male white rats. After the rats recovered, 100 of them were concurrently exposed to 435 MHz

pulsed RFEMF (1 μ s pulses at 1000 pps) in a special facility [Bonasera et al., 1988] for 22 h daily, 7 days a week, for 6 months. Samples of blood were assayed for the stress hormones ACTH, corticosterone, and prolactin in the plasma; plasma catecholamines; and hematologic parameters, including hematocrit and various blood cell counts. Also monitored were heart rates and arterial blood pressure. The results showed no significant RFEMF induced differences between exposed and sham exposed groups in any of those endpoints.

Human Studies

In an experimental study by de Seze et al. [1998], human volunteers were exposed to ultra high frequency (UHF) signals from GSM cell phones; and the levels of adrenocorticotropin, thyrotropin, growth hormone, prolactin, luteinizing hormone, and follicle stimulating hormone were assayed. No effects were found at levels currently encountered with these devices. However, the exposures were well below the thresholds determined in animal studies.

In summary, studies to date have shown no systemic effects on endocrine activity other than those that can be explained by heating and are analogous to a more generalized heat stress response.

EFFECTS ON BLOOD CELLS

Some early reports indicated that RFEMF might have specific effects on the blood and immune systems of mammals. Most reported effects were detected after exposure at power densities of about 10 mW/cm² and higher, but a few effects have been reported from exposure to levels as low as about 0.5 mW/cm². In most of the studies, the mechanisms for the effects were not investigated, and many of the results were not consistent with one another.

Erythrocytes (Red Blood Cells)

A number of studies were directed toward effects of RFEMF interactions with *in vitro* samples of erythrocytes [red blood cells (RBCs)] taken from animals or humans. Alterations of cell membrane function, particularly any effects on movement of sodium ions (Na⁺) and potassium ions (K⁺) across the membrane were sought.

The authors of several early Eastern European studies reported increased hemolysis (cell breakdown) and efflux of K⁺ from rabbit RBCs exposed to 1 or 3 GHz RFEMF at levels as low as 1 mW/cm². In a subsequent U.S. study [Peterson, 1979], heated samples of rabbit and human RBCs to 37 °C by exposing them to

2.45 GHz RFEMF and found an absence of hemolysis and K⁺ release for human RBCs.

Brown and Marshall [1986] sought nonthermal effects of RFEMF on growth and differentiation of the murine erythroleukemic (MEL) cell line. They exposed tubes of HMBA cultured MEL cells for 48 h to 1.18 GHz RFEMF at SARs of 18.5, 36.3, or 69.2 W/kg, with incubation temperature held at 37.4 °C. The results showed no significant differences in any of the three endpoints between the cultures exposed at each RFEMF level and their corresponding control cultures.

Leukocytes (White Blood Cells)

Studies were performed *in vitro* to determine whether exposure to RFEMF can stimulate lymphocytes (one type of leukocyte) to become lymphoblasts, that is, cells active in cell division (mitosis), and to undergo mitosis. In such studies, samples of lymphocytes taken from humans were cultured, exposed to RFEMF, and studied for effects. Usually such cells were cultured with a mitogen, an agent that stimulates cell transformation into lymphoblasts and mitosis. In some studies, more subtle effects on various types of leukocytes were sought. Hamrick and Fox [1977] exposed cultures of rat lymphocytes, and found the differences between the RFEMF and control cultures nonsignificant.

Lyle et al. [1983] sought effects for 60 Hz amplitude modulated 450 MHz RFEMF at 1.5 mW/cm² (SAR not stated) on the toxicity of certain rodent T-lymphocytes (effector cells) against lymphoma cells (target cells) of a specific type. The authors surmised that cytotoxicity was due to the action of the RFEMF on the effector cells. They also found that the mean percentage of cytotoxicity inhibition diminished with elapsed time after exposure. Mean cytotoxicity inhibition was negligible with unmodulated RFEMF; nonsignificant with 3, 16, and 40 Hz; maximal with 60 Hz; and significant (but smaller) with 80 and 100 Hz, indicating that the effects were due to the amplitude modulation itself. However, in the absence of data on SARs in the cell cultures on their spatial or variations over time, little if any credence is given to the findings of this study.

Sultan et al. [1983a] studied the effects of combined RFEMF exposure and hyperthermia *in vitro* on the ability of normal B-lymphocytes to cap surface immunoglobulin (I_g) following binding of specific antigen (anti-I_g) molecules. The authors concluded that the mechanisms responsible for inhibition of capping in their experiments are thermal in origin, observing no apparent effects of 2.45 GHz CW RFEMF if exposed and control samples are held at the same temperature. Sultan et al. [1983b] reported similar results with

suspensions of cells exposed for 30 min to 147 MHz RFEMF amplitude modulated at 9, 16, or 60 Hz. The authors stated, "The results demonstrate that at any of the modulation frequencies and power densities used, there was no significant difference in the percentage capping between the RFEMF treated cells and the controls as long as both were maintained at the same temperature ($P < .4$; Student's *t*-test)." They did discuss the various studies on amplitude modulated fields, but obviously did not find any effects ascribable to the modulations per se.

Roberts et al. [1983] exposed human mononuclear leukocyte cultures to 2.45 GHz RFEMF for 2 h at 4 W/kg. The differences among the groups were not significant. Similar results were obtained at 0.5 W/kg and intermediate SARs. There were also no significant differences among the groups in DNA, RNA, and total protein synthesis. In a later study, Roberts et al. [1987] infected human mononuclear leukocyte cultures with influenza virus and then exposed them to 2.45 GHz RFEMF, either CW or pulsed at 60 or 16 Hz (duty cycle 0.5), all at 4 W/kg. Control cultures were sham exposed. No significant differences due to RFEMF exposure relative to sham exposure were found in leukocyte viability of virus infected cultures, or uninfected cultures, or in DNA synthesis from mitogen stimulation.

Cleary et al. [1985] exposed rabbit neutrophils (another type of leukocyte) within a temperature controlled coaxial exposure chamber to 100 MHz CW RFEMF for 30 or 60 min and showed that the viability and phagocytotic ability of the neutrophils were not affected by such RFEMF exposures.

Kiel et al. [1986] sought effects of RFEMF on the nonphosphorylating oxidative metabolism of human peripheral mononuclear leukocytes (mostly lymphocytes). They noted that production of active oxygen metabolites is accompanied by the generation of chemiluminescence (CL) and that CL can be enhanced by addition of luminol and used as a sensitive detector of such effects. The authors noted that the CL variability among the 15 donors was large, but that nevertheless the CLs for both the RFEMF exposed and sham exposed samples significantly exceeded those for their respective incubator held controls. However, the difference in mean CL between the RFEMF exposed and sham exposed samples was not significant.

Effects on Immunological Function

Huang and Mold [1980] exposed mice to 2.45 GHz RFEMF at 5–15 mW/cm² (3.7–11 W/kg) 30 min per day for 1–17 days, after which spleen cells were cultured with or without a T-lymphocyte mitogen or a B-lymphocyte mitogen. The radiotracer tritiated

thymidine was added during culturing. After culturing, the cells were assayed for thymidine uptake, a measure of DNA synthesis during cell proliferation.

Plots of thymidine uptake versus exposure duration showed responses that varied cyclically with time for cells from both mitogen stimulated and nonstimulated cultures. However, similar plots for sham exposed mice also showed cyclical fluctuations, apparently due to factors other than RFEMF. Therefore, whether RFEMF per se has cell proliferative effects could not be ascertained in this study. In another part of the study, exposure at 15 mW/cm² (11 W/kg) for 5 days (30 min per day) did not diminish the cytotoxic activity of lymphocytes on leukemic cells injected after, or concurrently with, the last exposure.

Wiktor-Jedrzejczak et al. [1977] studied mice exposed to 2.45 GHz RFEMF at SARs of up to 14 W/kg. Taken together, the results of this study show that thermogenic RFEMF levels, for example, 14 W/kg, can have weak stimulatory effects on splenic B-lymphocytes but none on T-lymphocytes.

Sulek et al. [1980] found that the threshold for increases in CR⁺ B-cells was about 5 W/kg for 30 min exposures to 2.45 GHz RFEMF, yielding an energy absorption threshold of 10 J/g. They also found that multiple exposures at levels below the threshold were cumulative if done within 1 h of one another, but not if spaced 24 h apart, even if the sum of the energy absorption values exceeded the threshold.

Smialowicz et al. [1981] exposed 16 rats almost continuously for 69–70 consecutive days to 970 MHz RFEMF at 2.5 W/kg. There were no significant differences between RFEMF exposed and sham exposed rats in erythrocyte count, total or differential leukocyte counts, mean cell volume of erythrocytes, hemoglobin concentration, or hematocrit.

Smialowicz et al. [1982] exposed mice to CW or pulsed 425 MHz RFEMF at SARs up to 8.6 W/kg. No differences were seen in mitogen stimulated responses of lymphocytes or in primary antibody response to sensitization with SRBC or another antigen (PVP) between RFEMF exposed and sham exposed mice or between mice exposed to the CW or pulse modulated RFEMF.

Galvin et al. [1982] exposed groups of rats to 2.45 GHz RFEMF for 8 h at 2 or 10 mW/cm² (0.44 or 2.2 W/kg). A sham exposed group served as controls. Within 5–15 min after treatment, peritoneal mast cells were extracted from rats of each group, and mitogen induced histamine releases from these cells were determined. The results showed no significant differences among the three groups in percentage of cell viability, percentage of cells, amount of histamine per cell, and cell diameter. For groups of rats similarly

exposed, the total red and white cell counts were not affected by the 8 h exposure at either RFEMF level, nor were blood hemoglobin levels or percentages of lymphocytes and neutrophils relative to those of the sham group. The other types of cells were also unchanged by the RFEMF. Serum biochemistry parameters were not affected by either RFEMF level.

Wong et al. [1985] noted that relatively few studies had been done in the HF band (3–30 MHz), that most such studies showed that thermogenic levels of RFEMF were necessary for significant effects of acute exposure, and that possible effects of prolonged exposure to low RFEMF levels in that frequency range were not investigated. Toward the latter purpose, they conducted two experiments with rats at 20 MHz.

In the first experiment, 200 rats were caged in 40 groups of five rats. Twenty of the groups were exposed to 20 MHz RFEMF at 1920 mW/cm^2 (about 0.3 W/kg) for 6 h per day, 5 days per week; and the other 20 groups were sham exposed as controls. After 8 days of treatment, six groups each of exposed and control rats were euthanized and examined for histopathology. This was also done for seven groups after 22 days and for the remaining seven groups after 39 days.

In the second experiment, 24 rats were divided into exposed and control groups of 12 each, but each rat was housed separately and all rats were euthanized after 6 weeks. Blood samples were collected and routine counts and blood chemistry assays were done. The spleens were then excised and weighed, and suspensions of spleen cells were prepared. Various other tissues were also examined for histopathology.

The first experiment yielded a significantly higher mean RBC count and a significantly lower mean hemoglobin content for the rats terminated after 39 days of exposure than for the control group, but the statistical analysis showed that those differences were not RFEMF related. In the second experiment, however, no significant differences were seen in RBC count, hemoglobin, or any of the blood chemistry parameters.

Regarding histopathology, the authors noted that rats examined for quality control before the start of the first experiment were normal, but pulmonary congestion and edema, rhinitis, and peribronchiolar and pulmonary perivascular lymphoid proliferation were evident by day 8. In addition, emphysema and incomplete lung expansion were present in some rats killed on day 22. However, no pattern of lesions could be attributed to the RFEMF exposure. Focal disseminated pneumonia was present in 4 exposed and 4 control rats of the first experiment euthanized on day 39; but of the 200 rats used in that experiment, only one had any clinical symptoms of illness. All 24 rats in the second

experiment were histologically normal at the end of the 6 week period of exposure.

EFFECTS ON CARDIOVASCULAR SYSTEM

Paff [1963] investigated the possibility of direct effects of RFEMF on the heart. They exposed isolated hearts of 72 h old embryonic chicks. Thermal damage was evident at high exposures, but consistent effects on the ECG were seen in the absence of thermal damage at lower levels. Subsequently several investigators reported chronotropic effects of RFEMF exposure which could be altered by the application of pharmacological agents.

Whilst some early *in vitro* studies were equivocal, later research concluded that the chronotropic effects seen were systemic or centrally initiated whole body responses involving the sympathetic or parasympathetic nervous systems. Changes that do occur at high power densities appear to result from systemic hyperthermia, although some effects, including bradycardia may result from high SAR in the brain resulting from nonuniform absorption. D'Andrea et al. [1980] studied the physiological effects of prolonged exposure to 915 MHz in rats at a whole body SAR of 2.5 W/kg for 16 weeks and found no change in heart weight at exposure end.

Toler et al. [1988] found no change in resting heart rate or mean arterial blood pressure after 6 months exposure to 435 MHz RFEMF, modulated with $1 \mu\text{s}$ pulses at 1 kHz, with a power density of 10 W/m^2 and at an estimated whole body SAR of 0.35 W/kg .

Jauchem et al. [1983] determined by parasympathetic blockade with atropine that thermal bradycardia seen in rats was not as a result of vagus nerve activity. In a subsequent study, Jauchem et al. [1985] found that the administration of a phenothiazine drug (chlorpromazine) could counteract the hyperthermia caused by RFEMF absorption. In an important review, Jauchem [1997] concluded that in general, if tissue is not heated during exposure, current flow appears to be necessary for major cardiovascular effects to occur. Jauchem also reported that despite a much greater increase in subcutaneous temperature, the general pattern of cardiovascular changes during 35 GHz RFEMF induced hyperthermia was comparable to changes at lower RFEMF frequencies. Acute cardiovascular changes in humans deliberately exposed to RFEMF are documented in studies relating to magnetic resonance imaging (MRI) and, at higher levels, of RFEMF used to deliberately destroy myocardial tissue in cardiac ablation therapy.

Soviet researchers reported indications that long term RFEMF may cause hypotension and bradycardia

or tachycardia, but these findings have not been replicated elsewhere in humans. Jauchem et al. [1999a,b] exposed rats to ultra wide band (UWB) pulses and reported no significant changes in heart rate or mean arterial blood pressure. However, Lu et al. [1999] reported a consistent induction of hypotension in rats from UWB electromagnetic pulses, an effect that persisted after exposure, without any commensurate change in heart rate. A potential source of confounding in this study may have been variation of experimental conditions between the exposure groups, since they do not appear to have been intermingled during the exposure period.

Recent human experimental studies have produced equivocal results regarding the possible interaction between RFEMF and blood pressure [Braune et al., 1998]. The net meaning of this evidence is that no effect has been established. The early reports of direct effects of RFEMF on myocardial and atrial tissue do not correlate with any effects seen when the heart is exposed *in situ*. Effects on heart rate are caused by systemic effects of noncardiac specific, usually whole body exposure, which may be influenced by nonuniform absorption.

CONCLUSIONS

An accumulated body of evidence published over the last three decades has identified, investigated, and quantified the responses of mammalian neuroendocrine and intercellular hormonal control systems to RFEMF exposure. In particular, the mechanisms for the production and control for corticosteroid, thyroid, and growth hormones have been extensively investigated. Hormones acting on reproductive tissues, including LH, FSH, and prolactin, have received less attention. Characterization of established effects show that they result from tissue heating, and are generally similar to nonspecific stress responses. There is an evident pattern in the *in vitro* literature of the thermal effect becoming more clearly identified as the only operative mechanism, and this trend is stronger as the technical precision of study methods improves. *In vivo* research in the 1980s has established thresholds of effects, initially in small mammals, and later in primates. Whilst interactions between circadian variations and intrinsic effects from RFEMF have been identified and characterized, the levels of effects, defined in terms of SAR, have been confirmed with coherence and consistency. Such findings provide a useful basis for setting RFEMF exposure standards.

The pineal gland and its production of melatonin has often been considered a candidate for possible sensitivity to electromagnetic fields (EMFs) at wave-

lengths outside the RFEMF range and arising from mechanisms other than thermal, because of the gland's established response to the visible part of the EMF spectrum. However, this established response is generally accepted to be activated by the light sensitivity of the retina. Whilst there is relatively little research on the pineal and RFEMF, the existing data can only be interpreted as showing no effect. These research findings are reinforced by the results of the previously discussed studies by Guy, Toler, and their respective coworkers in which animals are exposed to RFEMF over their lifetimes. In those two important studies, no adverse effects have been found in hormone levels. One recent human study on cell phone exposures reported no deleterious effects at partial body exposures levels within current exposure standards. However, further research on this topic is continuing.

Studies on RFEMF exposure of erythrocytes initially reported increased cell breakdowns, but later studies indicated no effect at very high SARs (over 60 W/kg), provided temperature was controlled. Studies of RFEMF exposure of leukocytes and on immunological function indicate effects at relatively low levels, but these are likely to be of thermal origin. The possibility of direct (i.e., nonthermal) effects of RFEMF on cardiovascular tissue has been investigated, and the results indicated that either tissue heating or inadequate cooling by current flow was involved. Cardiovascular function can also be affected indirectly by local heating of brain tissue. An exception to this absence of cardiovascular effect may be in the case of exposure to UWB band RFEMF. Recent human experimental studies have produced equivocal results regarding RFEMF exposure and measured blood pressure in normal human experimental studies, but the most recent publication has neither demonstrated nor confirmed any effect [Braune et al., 2002]. However, in all considerations of possible effects of RFEMF on homeostasis and regulatory systems, the possibility of interaction or interference with the mechanism on which a therapeutic process depends must be considered. Whilst this has not yet been substantially studied for drugs in the cardiovascular system, there are no indications of adverse effects.

Whilst the literature retains numerous studies with unconfirmed findings as well as some, which are contradictory, these are not suitable for use in health protection. However, there is sufficient coherent data on which to base thresholds for human exposure safety standards. Overall, the body of published literature on the bioeffects of RFEMF to the humoral and endocrine systems does not provide any valid experimental basis to alter acceptance of 3–4 W/kg as the threshold on which to base exposure standards to protect against adverse human health effects.

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