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Microwave Effects on the Nervous System

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Studies have evaluated the electroencephalography (EEG) of humans and laboratory animals during and after Radiofrequency (RF) exposures. Effects of RF exposure on the blood–brain barrier (BBB) have been generally accepted for exposures that are thermalizing. Low level exposures that report alterations of the BBB remain controversial. Exposure to high levels of RF energy can damage the structure and function of the nervous system. Much research has focused on the neurochemistry of the brain and the reported effects of RF exposure. Research with isolated brain tissue has provided new results that do not seem to rely on thermal mechanisms. Studies of individuals who are reported to be sensitive to electric and magnetic fields are discussed. In this review of the literature, it is difficult to draw conclusions concerning hazards to human health. The many exposure parameters such as frequency, orientation, modulation, power density, and duration of exposure make direct comparison of many experiments difficult. At high exposure power densities, thermal effects are prevalent and can lead to adverse consequences. At lower levels of exposure biological effects may still occur but thermal mechanisms are not ruled out. It is concluded that the diverse methods and experimental designs as well as lack of replication of many seemingly important studies prevents formation of definite conclusions concerning hazardous nervous system health effects from RF exposure. The only firm conclusion that may be drawn is the potential for hazardous thermal consequences of high power RF exposure. Bioelectromagnetics Supplement 6:S107–S147, 2003. Published 2003 Wiley-Liss, Inc.†

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INTRODUCTION

The human body has billions of neurons in its central nervous system (CNS) and peripheral nervous system [Kandel et al., 2000]. The CNS includes the brain and the spinal cord. Neurons are supported by other cell types such as glia cells, which support and nourish the nearby neurons. The nervous system is constantly reacting and adjusting to changes (stimuli) in both the outside environment and internal changes within the body in order to maintain equilibrium. Reaction to stimuli generates impulses, which through the peripheral nerves and CNS are analyzed, compared, combined, and coordinated. When responding to a stimulus, such as pressure, temperature, or chemical, a potential (i.e., generator potential) is initiated at the receptor, from which a nerve impulse is propagated through the nerve axons and synapses to the CNS. Responses from the CNS are transmitted to the effectors, such as muscles or glands, to adjust to the stimulus. Signal transmission is accomplished through complicated electrical and chemical events. Many kinds of neurotransmitters exist in the nervous system. Since there is tremendous electrical activity in neural transmission, the nervous system was thought to be the most sensitive to electromagnetic (EM) exposure. Therefore, there were extensive studies in the 1960s and 1970s of EM exposure effects on the nervous system and human behavior [see review by Elder and Cahill, 1984]. The recent concerns in the 1990s on cellular telephone safety have revived interest in handheld mobile telephone and base station effects on human brain tissues.

This article presents an overview of the recent RF bioeffects literature dealing with the nervous system, in an effort to discover if other mechanisms not based on thermal events, may be sufficiently supportive as a basis for setting exposure standards. Considering the sizable literature not all articles dealing with nervous system effects can be included. The most important criterion is the importance of any study delineating characteristics of exposure that could be harmful to humans.

Sections of the article begin with a brief discussion of neural science to introduce the topic to readers unfamiliar with that subject matter. Also, for each section a Table summarizes many of the studies published after 1980.

CENTRAL NERVOUS SYSTEM (CNS)

Due to large differences in microwave (MW) safety standards between the United States and Soviet Union in early 1970s, a program was established in 1975 for the collaborative study of the biological effects of physical factors in the environment. One of the topics that were included in this problem area was the effect of nonionizing radiation on the CNS and behavior. In the 1970s, research efforts were primarily concerned with MW effects on electroencephalography (EEG), evoked responses, morphology, and neural responses. Since then, many studies have been conducted on blood–brain barrier permeability, calcium efflux, neurochemistry, and the interaction of drugs with microwaves and cognition.

Electroencephalography and Evoked Responses

The electroencephalogram (EEG) is generated in the cortex by the flow of synaptic currents through the extracellular space. The EEG records the collective activity of many hundreds of thousands of neurons through electrodes placed on the surface of the scalp. The EEG is distorted by the filtering and attenuation produced by intervening layers of tissue and bone, which act like resistors and capacitors in an electric circuit. Thus the amplitude of EEG potentials (microvolts) is much smaller than the voltage changes in a single neuron (millivolts). The surface EEG predomi-

nantly reflects the activity of cortical neurons close to the EEG electrode. Thus deep structures such as the hippocampus, thalamus, or brain stem do not contribute directly to the surface EEG. The EEG provides important indices for studying arousal, wakefulness, sleep and dreaming, and for diagnosing epilepsy and coma.

The human EEG changes according to a 24 h circadian rhythm of behavior in response to the 24 h astronomical cycle. Sleep states form the unconscious part of that cycle lasting approximately 8 h during night. A basic principle of sleep cycle control in humans is articulated in Borbély [2001]: ''Two Process Model,'' in which sleep–wake state transitions result from the combined effects of circadian factors (process C) and homeostatic factors (process S) [Borbély and Achermann, 2000]. During sleep, a third regulator, the ultradian, REM–NREM [rapid eye movement (REM) and non-REM sleep (NREM)] oscillator comes into play [Pace-Schott and Hobson, 2002]. The 90 min REM–NREM cycle of adult human sleep is an ultradian rhythm.

Molecularly, the circadian rhythm of sleep involves interlocking positive and negative feedback mechanisms of circadian genes and their protein products in cells of the suprachiasmatic nucleus that are entrained to ambient conditions by light. Circadian information is integrated with information on homeostatic sleep need in nuclei of the anterior hypothalamus. These nuclei interact with arousal systems in the posterior hypothalamus, basal forebrain, and brainstem to control sleep onset. During sleep, an ultradian oscillator in the mesopontine junction controls the regular alternation of REM and NREM sleep. Sleep cycles are accompanied by neuromodulatory influences on forebrain structures that influence behavior, consciousness, and cognition [Pace-Schott and Hobson, 2002].

EEG frequencies are conventionally subdivided into approximate frequency bands related to these three oscillation rhythms. The exact limits of the frequency bands of α, β, δ, θ, and γ appear to be fuzzy, with every author taking some liberty with the ranges. One example classifies brain waves into α: 8–13 Hz (relaxed 10 Hz, NREM sleep spindles 12–14 Hz); β: 13–30 Hz; and γ: 30–80 Hz (awake or REM 16–25 Hz); δ: 0.5–4 Hz (NREM 0.5–2 Hz); θ: 4–7 Hz (drowsiness) [Kandel et al., 2000].

In the waking EEG, we see that the brain is activated to allow behaviors which can interact with conditions of the outside world and it is modulated to capture important information. In NREM sleep, the brain is actively off-line, allowing stereotyped endogenous activation to be initiated in the forebrain. This mechanism could allow recent inputs such as corticopetal information outflow from the hippocampus to be reiterated in a manner that promotes plasticity processes that are associated with memory consolidation. In REM sleep, the brain is reactivated but the microchemistry and regional activation patterns are markedly different from those of waking and NREM sleep. Cortically consolidated memories, originally stored during NREM by iterative processes, would thus be integrated with other stored memories during REM [Maquet, 2001; Hobson and Pace-Schott, 2002].

There are strong indications that sleep has thermoregulatory functions. Body and brain temperatures are usually reduced during sleep. Heating the hypothalamus induces sleep in animals, and body heating prior to sleep increases subsequent slow wave sleep in humans [Kandel et al., 2000]. During NREM, sleep neuronal activity is low, and metabolic rate and brain temperature are at their lowest. In addition, sympathetic outflow decreases and heart rate and blood pressure decline. Conversely, parasympathetic activity increases and then dominates during the NREM phase, as evidenced by constriction of the pupils. Muscle tone and reflexes are intact [Hobson and Pace-Schott, 2002]. During NREM sleep, significant regional declines in glucose or oxygen use relative to waking occur in the pons, thalamus, hypothalamus, and caudate nucleus as well as in lateral and medial regions of the prefrontal cortex [Maquet, 1995; Braun et al., 1997, 1998; Maquet et al., 1997].

Decreased blood flow in the thalamus and in the prefrontal and multimodal parietal association cortices accompanies the onset and deepening of NREM sleep. During REM sleep, blood flow increases but dorsolateral prefrontal areas remain less active than in waking [Andersson et al., 1998; Kajimura et al., 1999; Maquet, 2000; Nofzinger et al., 2000].

Deactivation of executive areas in the dorsolateral prefrontal cortex during NREM sleep followed by their failure to reactivate during REM, might underlie the prominent executive deficiencies of dream mentation, including disorientation, illogic, impaired working memory, and amnesia for dreams [Hobson and Pace-Schott, 2002].

Animal studies. In the 1960s and 1970s, scientists in both Eastern European countries and the United States had reported the alteration of EEG and evoked responses in animals exposed to RF fields [Bawin et al., 1960; Kholodov, 1963; Baranski and Edlwejn, 1967; Johnson and Guy, 1972; Bawin et al., 1973]. Taylor and Ashleman [1975] showed that a decrease in latency and amplitude of the monosynaptic ventral root reflex of a cat spinal cord exposed to 2.45 GHz microwaves can also be produced by raising the temperature of the perfusion solution. Sensory evoked responses will be

discussed in a later section. Exposure associated changes in EEG are summarized in Table 1.

The use of metallic electrodes for EEG recordings made most results questionable. Johnson and Guy [1972] demonstrated thermographically that the presence of a metallic electrode in a cat brain increased the local specific absorption rate (SAR) by 50 times. Glass electrodes filled with Ringers solution [Johnson and Guy, 1972] or carbon-loaded Teflon electrodes with conductivities similar to tissue [Tyazhelov et al., 1977; Chou and Guy, 1979] were used to minimize perturbation. EEG electrodes pick up RF fields and induce current into the head. It is difficult to differentiate between the direct effect of the RF field and any effects of the induced currents.

The initial results of the US-USSR collaborative study were reported by McRee et al. [1979] of the United States, who showed that experiments with Sprague–Dawley rats exposed to 425 MHz 10 mW/cm^2 exposure, 12 days after breeding, and to 2.45 GHz 5 mW/cm^2, 6 days after breeding, produced no statistical differences between the control and treatment groups in the histogram and power spectral analyses performed on spontaneous EEG segments. The USSR team reported their study on 24 rabbits, continuously radiated (7 h per day) for 3 months at 10, 50, and 500 μW/cm^2 [Shandala et al., 1979]. Changes in bioelectric activity were noticed, as well as disturbances in the EEG frequency spectrum. Verifiable decreases in the number of δ range oscillations and an increase in α and β range potentials were also observed. No significant changes were seen in the EEGs of the control animals. Procedures for these two studies were completely different and therefore the results are not comparable. Consequently, an agreement was made to work on an experiment with the same protocol. In 1989, Mitchell et al. reported the results of a joint project performed by the National Institute of Environmental Health Sciences in the United States and the Marzeev Research Institute of General and Communal Health of the USSR [Mitchell et al., 1989]. A group of male Fisher 344 rats was exposed dorsally in the far field of a horn antenna to 2.45 GHz at 10 mW/cm^2 (average SAR 2.7 W/kg) for 7 h. Saline solution filled glass electrodes were used to record cortical EEG and evoked potentials. Both groups found statistically significant effects in the power spectral analysis of EEG frequency, but results from the two groups were inconsistent. This failure of both groups to substantiate the results of the other reinforces the importance and necessity of replication through duplicate projects.

Another notable study was that of Takashima et al. [1979]. They reported on the effects of modulated RF field effects (1–30 MHz, 15 or 60 Hz modulation) on male rabbit EEGs following acute (2–3 h) and chronic (2 h for 4–6 weeks) exposures. While acute exposure up to 500 V/m did not cause effects, chronic exposure above 90 V/m enhanced the low frequency components of the EEG and decreased high frequency activities. The study showed that metal electrodes did cause artifacts during recording. However, the effects of chronic exposure were not due to the presence of electrodes.

Kaplan et al. [1982] exposed pregnant squirrel monkeys to 2.45 GHz fields (SAR up to 3.4 W/kg). No differences in EEGs were seen between exposed and sham dams and infants. In a high intensity pulsed microwave (PW) exposure of the rat head; Guy and Chou [1982] did not observe obvious EEG changes 2 min after a 915 MHz MW exposure at 25.8 kJ/kg for 0.1 s. The temperature rise in the brain could reach 8.4 °C. Carbon loaded Teflon electrodes were used for EEG recording. At 20 s after exposure, the EEG amplitude increased several fold but recovered within 2 min.

Chizhenkova [1988] reported that the heads of unanesthetized rabbits exposed to 2.4 GHz for 1 min at 40 mW/cm^2 demonstrated EEG spindle-shaped firings and an increase in the number of slow waves. These were accompanied by both an increase and decrease in the pulse frequency of the neurons. These changes were observed in 41–52% of the cases. Glass electrodes filled with 2.7 M NaCl solution were used for recording. After MW exposure, an enhancement of evoked responses was observed in the visual cortex neurons to single light flashes in 61% of the cases. The MW field facilitated the driving response to light flashes in 80% of cases, as was shown by a decreased threshold for obtaining evoked potentials and by the widening of the frequency range to which the neurons were able to respond. The evoked activity was a more sensitive indicator of the MW effect than the unstimulated brain activity. The reactivity alterations were more easily detected when using the driving response test than by using single stimuli.

Vorobylov et al. [1997] exposed unanesthetized rats to 945 MHz 0.1–0.2 mW/cm^2 amplitude modulated at 4 Hz, for 1 min on and 1 min off for 10 min. Effects on the EEG recorded with carbon electrodes were studied. There were no differences other than an elevation of EEG asymmetry in 10–14 Hz range observed during the first 20 s after onset of the MW field. Control conditions are in question, especially the positive controls such as pulsed sounds.

In acute experiments on rats, changes were seen in EEG and cerebral blood flow (CBF) upon MW exposure [Thuroczy et al., 1994]. A whole body exposure of 30 mW/cm^2, 2.45 GHz continuous wave (CW) for 10 min caused an increase in the total power of the EEG

TABLE 1. Effects of RF Exposure on Electroencephalography (EEG)

EMF effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
Increase number of spindle-shape activity firings and slow waves; enhance evoked responses in the visual cortex neurons to single light flashes	Rabbits (unanesthetized)		2400	CW	40	1 min	Chizhenkova [1988]
Significant effects in the power spectral analysis of EEG frequency, but not at the same frequency	Rats	2.7	2450	CW	10	7 h	Mitchell et al. [1989]
Significant elevations of EEG asymmetry in 10–14 Hz range during the first 20 s	Rats 8		945	(AM: 4 Hz) 2 ms pulse duration	0.1–0.2 mW/cm antenna 28–30 cm above rat	1min on:1min off alternating for 10 min	Vorobylov et al. [1997]
Total power of spectra no change	Rats 40		2450	1 min	1030	10 min	Thuroczy et al. [1994]
Increase in the power of the δ waves	Rats	42	4000 CW	AM: 16 Hz		30 min	Thuroczy et al. [1994]
Increase in the power of β waves	Rats	8.4	4000	CW			Thuroczy et al. [1994]
Temporary changes in brain wave and behavior	Human 10		0.1–960 MHz CW; 8.5–9.6 GHz pulse mod		<1 pW/cm̈		Bise [1978]
Significant sleep inducing effect	Human 52: 32 females, 20 men 18–53, median 24 years	<10 in oral mucosa and 0.1 W/kg in brain	27.12	Intrabuccalamplitude modulated 42.7 Hz		3 s on:1 s off for 15 min	Reite et al. [1994]
Significantly reduced sleep onset and spectral power of NREM slow wave sleep increase in the 10–11 and 13.5–14 Hz bands in initial part of sleep only	Human right handed men 20–25 (mean 22 years)	Max1 W/kg over 10 g	GSM 900; linear polarized	2, 8, 217, 1736 Hz; 87.5 % duty cycle (vs. 12.5% for mobiles)	Three antenna 30 cm away	One night 11 pm–7 am alternating 15-min on:15-min off	Borbély et al. [1999]
Spectral power of the EEG in NREM sleep was increased in first 30 min of sleep only. The maximum rise occurred in the 9.75–11.25 Hz and 12.5–13.25 Hz bands during the initial part of sleep (α band). No effect on sleep latency or sleep stages or REM sleep spectrum. Same effect whether exposure was from the left or right side	16 Right handed-human: men 20–25 (mean 22 years)	Spatial peak 0.5 W/kg over 10 g. Hemi-brain 0.14 W/kg	900 MHz: CW and GSM "Synthesized base station like signals" (cocktail)	2, 8, 217, 1736 Hz; 87.5 % duty cycle	Unilaterally left or right side 11 cm from the head	30 min preceding 3 h daytime sleep episode recording	Huber et al. [2000]
The present results seem to show that (1) pm-EMF alters waking rCBF and (2) pulse modulation of EMF is necessary to induce waking and sleep EEG changes	2× 16 Human male right-handed (20–25 yrs)	Spatial peak 1 W/kg over 10 g. (4× higher than basesite ex.)	Ex 1 and 2: 900 MHz handset signal; Ex 2. 900 MHz CW	Ex 1 and 2: 12.5% duty cycle, 2, 8, 217, 1736 Hz, +harmonic	Planar antennas, unilaterally left side 11 cm from the ear	Ex 1: 8:00–14:00 h 30 min left side of head: then 10 min delay before PET: awake counting	Huber et al. [2002]
Scalp electrodes (occipital) O1/O2. During and after exposure for some hours the O2 position α wave is altered (increased energy)	Human: 17 men and women 20–27 years		150 MHz and (magnetic field coils at the neck, 10-8 T)	217 Hz, pulse width 4.6 ms, interrupts 10 μs	At brain 6 cm depth: 1 μW/cm^2	Exposed 2–3× for 15 min	Von Klitzing et al. [1995]

(*Continued*)

TABLE 1. (*Continued*)

EMF effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
In relaxed awake subjects there was increase in EEG power in α 2: 9.75–12.5; β1 and 2 with a delay of 15 min after exposure. (Mega Wave caused increase in EEG power during and after exposure in α 2: 9.75–12.5; β1 and 2)	Humans: 36 male and female	Similar to 0.25 W phone	902.4 MHz GSM 8 W; (and 150 MHz Mega Wave therapy device)	217 Hz pulse freq, (80 μs 9.6 Hz)	Magnetic flux density in the range of 400 pT	1 h 6 min	Reiser et al. [1995]
During RF exposure, significant suppressive effect on REM sleep and increased REM EEG spectral power (α mainly affected) density and shortening of sleep onset (NREM)	Human: 14 males (mean 27 years)		900 GSM mobile phone	217 Hz, pulse width 580 μs	0.05 at 40 cm	8 h, 3 night	Mann and Röschke [1996]
No short term effects of digital mobile phone telephone on the awake closed eye EEG with special attention to the spectral power density of the α (8–13 Hz) EEG	Human: 34 males (mean 27 years)		900 GSM mobile phone	217 Hz, pulse width 580 μs	0.05 at 40 cm	3.5 min	Röschke and Mann [1997]
No (CNS-mediated) effects on heart rate variability during human sleep	Human: 12 males (21–34 years)		900 GSM mobile phone	217 Hz, pulse width 580 μs	0.05 at 40 cm	8 h, 1 night	Mann et al. [1998]
Suppression of REM sleep as well as a sleep-inducing effect; previous results could not be replicated; might be due to dose dependent effects of the EMF on the human sleep profile	Human: 24 healthy males 18–37 years (mean 26 years)	0.3 to Max 0.6 W/kg	Circular polarized 900 MHz GSM	217 Hz, pulse width 577 μs	0.2 W/m^2	8 h, 1 night 11 pm–7 am	Wagner et al. [1998]
No effects on human EEG activity recorded in an awake, closed-eyes situation. Exposure to one of the phones caused a statistically significant change in the absolute power of the δ recording probably due to statistical chance	Human: 10 men 28–48 years and 9 women 32–57 years		Five cellular phones (anal and digital 900 MHz or 1800 MHz)	900 NMT, GSM; PCN 1800 MHz,	Peak power 1–2 W, transmit at max power		Hietanen et al. [2000]
Effect with task-relevant target stimuli in the EEG band 18.75–31.25 Hz (β/γ/ awake). No effect with irrelevant standard stimuli	Human: 13 healthy males 21–27 years		916.2	217 Hz pulse freq, pulse width 577 μs radiated power of aerial 2.8 W		Around 10 min with exposure to left posterior temporal region	Eulitz et al. [1998]
Significant decrease in preparatory slow brain potentials (SP) in awake visual monitoring task at central and temporo-parietal–occipital regions but not frontal. No effects on finger movement and contingent negative variation task	Human: 16 healthy right-handed males 21–26 years	0.882 W/kg over 10 g	916.2	217 Hz pulse freq, pulse width 577 μs radiated power of aerial 2.8 W		Around 10 min: telephone at left ear	Freude et al. [1998]
Significant decrease in awake slow brain potentials (SP) in a complex visual task. No effects on finger movement and contingent negative variation task	Human: 20 healthy right-handed males 21–30 years	2.8 W/kgover 10 g	916.2	217 Hz pulse freq, pulse width 577 μs radiated power of aerial 2.8 W		Around 10 min: telephone at left ear	Freude et al. [2000]
One-hour exposure to mobile phone RF EMG has no effect on auditory brainstem responses (ABRs) and distortion products otoemission (DPOE) recordings in the conditions of their protocol	10 men 10 women (20–30 years)		900	217 Hz GSM	Full power peak power 2 W/8 duty cycle 1/8	60 min exposure	Thimonier et al. [1999]

Effects of microwaves (MW) (900 MHz) on the cochlear receptor: exposure systems and preliminary results. No effect of exposure was found on otoacoustic emissions from the cochlea	S–D rats, N = 8 per group	Head 0.2 or (a) 1.0 W/kg, (b) 1.0 W/kg	(a) 950, (b) 936	CW	Far-field exposure	(a) 3 h/day for 3 days or (b) 3 h/day for 5 days	Marino et al. [2000]
Results suggest that the exposure to EMF does not alter the resting EEG per se but increases EEG relative power of 8–10 Hz significantly during auditory memory tasks (words) during retrieval but not during resting	8 Males and 8 females right handed (mean 22 years)		902 GSM	217 Hz, pulse width 577 μs, 0.25 W	Normal use position right side of head	Dimmed room, in chair, 30 min exp	Krause et al. [2000a]
There was no main effect of EMF at any frequency band between the event related synchronous (ERS) and desynchronous responses (ERP elicited by targets and non targets, reaction time or accuracy on a visual sequential letter task 'N-back'	24 Right handed adults M/F 20–30 (mean 23 years)		902 GSM	217 Hz, pulse width 577 μs, 0.25 W	Normal use position right side of head	Dimmed room, in chair, 30 min exp	Krause et al. [2000b]
MP RF may suppress the excessive sleepiness and improve performance while solving a monotonous cognitive task requiring sustained attention and vigilance	22 Narcolepsy-cataplexy pts mean 48 years	0.06 W/kg over 10 g	900 Motorola d520 MP	217 Hz, pulse width 577 μs, 2,8 Hz 0.25 W		45 min right ear	Jech et al. [2001]

spectrum. At 10 mW/cm^2, no changes were observed. CBF, however, did increase after the 10 mW/cm^2 exposure. A localized brain exposure, 4 GHz CW at 42 W/kg induced an increase in the power of EEG δ waves (0.5–4 Hz). Amplitude modulation at 16 Hz and 8.4 W/kg SAR caused an increase in the power of EEG β waves (14.5–30 Hz), but no changes in CBF were seen. Continuous wave exposure at 8.4 W/kg increased CBF, but the EEG spectrum was unaffected. At the high exposure levels, heating of brain was expected.

Human studies. Bise [1978] reported a pilot study of MW exposure with power densities lower than 1 pW/cm^2 on ten human subjects. Temporary changes were seen in brain wave patterns and in the subjects' behavior. Exposure frequencies ranged from 0.1–960 MHz CW and pulse modulated from 8.5 to 9.6 GHz. This study was considered unacceptable since no others were able to demonstrate MW EEG effects in humans or animals at 1 pW/cm^2 and the level is orders of magnitude below the environmental level [Tell and Mantiply, 1980].

Reite et al. [1994] investigated the sleep inducing effect of a Low Energy Emission Therapy device (LEET) that emitted a 27.12 MHz signal amplitude modulated at 42.7 Hz over a duration of 15 min, intermittently (3 s on:1 s off) intrabuccally (SAR 10 W/kg at buccal mucosa). The exposure resulted in a significant sleep inducing effect in subjects. This sleep inducing effect would most likely be due to heat in the region of the anterior hypothalamus that is located in the base of the brain above the palate where the emitting device was located.

To investigate whether electromagnetic fields (EMF) emitted by digital mobile phones (MP) affects the brain during sleep, Borbély et al. [1999] exposed healthy, young subjects during an entire night-time sleep episode to an intermittent exposure schedule (900 MHz GSM; with modulations at 2, 8, 217, and 1736 Hz maximum head SAR 1 W/kg at a 87.5% duty cycle) consisting of alternating 15 min on–15 min off intervals. Behind each bed was an array of 3-dipole antennas 30 cm from the head of a recumbent subject. Compared with a control night with sham exposure, the amount of waking after sleep onset was reduced by 18–12 min. Spectral power of the EEG in NREM was increased. The maximum rise occurred in the 10–11 Hz and 13.5–14 Hz bands during the initial part of sleep and then subsided. The results demonstrate that pulsed high frequency EMF in the range of radiotelephones may promote sleep and modify the sleep EEG.

The aim of a study by Huber et al. [2000] was to investigate whether the EMF emitted by a 900 GSM digital antenna (11 cm from the right or left ear)

preceding sleep affects brain physiology at sleep onset and during the first 3 h of sleep. Sixteen healthy, young males were exposed for 30 min to EMF (900 MHz; spatial peak SAR 0.5 W/kg) during the waking period preceding sleep. They compared the control condition with sham exposure and found that spectral power of the EEG in NREM was increased. The maximum rise occurred in the 9.75–11.25 Hz and 12.5–13.25 Hz band during the initial part of sleep (α band). These changes correspond to those obtained in a previous study where EMF was intermittently applied during sleep. Stage II NREM occupies 50–60% of sleep in young adults and is characterized by distinctive sleep spindles (α: 12–14 Hz) and K complex waveforms, as well as a slow (<1 Hz) oscillation, which influences their timing [Kandel et al., 2000]. As a result, effects reported on sleep EEG are more likely to involve NREM α waves.

Huber et al. [2002] report that unilateral exposure on the right or left side of the head induced a similar EEG power distribution in the brain. These results demonstrate that exposure during waking modified the EEG during subsequent sleep but they failed to replicate the hypnotic effect of an earlier experiment [Borbély et al., 1999]. One effect that influences sleep over a whole night is heat [Kandel et al., 2000], and it could be a factor in this experiment.

Huber et al. [2000] suggest that since EEG power in the frequency range 12.75–14 Hz is largely determined by slow and fast sleep spindles [Werth et al., 1997], spindle generating mechanisms seem to be susceptible to EMF exposure. They suggest the similarity of EEG pattern with the left hemisphere EEG spectral power predominating, whether the exposure is on the left, or right side of the head may indicate a high susceptibility of subcortical structures such as the thalamus. Roth and Achermann [1999] point to a lateralization of noradrenergic innervation of the thalamus [Oke et al., 1978] but the noradrenergic innervation is not normally active during NREM sleep [Hobson and Pace-Schott, 2002].

There is further doubt that the effect can be a result of a high susceptibility of subcortical structures such as the thalamus since sleep spindles can be generated in the cortex alone [Steriade et al., 1993]. Their 87% duty cycle versus the usual GSM digital phone cycle of 12.5% may be a factor. Without replication by another laboratory we cannot rule out unknown factors including local heat, reflected RF, or some other unknown variables in the experimental paradigm as the cause. Roth and Achermann [1999] have shown that in the sleep records of 14 young right handed males, within the frequency (11–15 Hz) range of sleep spindles, power in NREM dominated in the left hemisphere in all derivations. In the centro-parietal derivation in the 4–8 Hz band, a right hemispheric predominance prevailed in NREM. This argues against lateralization. Roth and Achermann [1999] suggest that left–right differences may arise from structural and functional asymmetries of brain regions involved in the generation of the sleep EEG. But neither in the two most comprehensive recent reviews of sleep and cognition [Hobson and Pace-Schott, 2002; Pace-Schott and Hobson, 2002] is there an indication of structural or functional asymmetries of brain regions involved in the generation of the sleep, nor in the review in "Principles of Neural Science" [Kandel et al., 2000].

Effects of cellular telephone exposure on the EEG were reported by Von Klitzing [1995], Reiser et al. [1995], and Mann and Röschke [1996]. The fields were all pulsed 900 MHz, 217 pps. Human heads were exposed for 15 min to a headset at 40 cm spacing. An increase in α wave activity was observed immediately after exposure [Von Klitzing, 1995]. Reiser et al. [1995] observed an increase in α2 and β signals 15 min later. In a study by Mann and Röschke [1996], human volunteers were exposed for 8 h during nocturnal sleep. They found shortening of sleep and reduction of REM sleep duration. But the total sleep time and slow wave sleep were not affected. In a subsequent study, Röschke and Mann [1997] found no effect of digital mobile radiotelephone signals on the awake human EEG, including the α wave with 900 MHz EMF pulsed at a frequency of 217 Hz and with a pulse width of 580 μs, 0.05 mW/cm^2. The aim of this study was to illuminate the influence of digital mobile radiotelephone on the awake EEG of healthy subjects. For this purpose, they investigated 34 male subjects in a single-blind cross-over design experiment by measuring spontaneous EEGs under closed-eyes condition from scalp positions C3 and C4 and comparing the effects of an active (0.05 mW/cm^2) and an inactive digital mobile radio telephone (GSM) system. During exposure of nearly 3.5 min to the 900 MHz EM field pulsed at a frequency of 217 Hz and with a pulse width of 580 μs, they could not detect any difference in the awake EEGs in terms of spectral power density measures.

In another study Mann et al. [1998] investigated the influence of pulsed high frequency EMF emitted by 900 MHz GSM mobile telephones on heart rate during sleep in 12 healthy young males (21–34 years). Beside mean RR interval (distance between two electrocardiogram waves) and total variability of RR intervals based on calculation of the standard deviation, heart rate variability was assessed in the frequency domain by spectral power analysis, providing information about the balance between the two branches of the autonomic nervous system. For most parameters, significant dif-

ferences between different sleep stages were found. For all heart rate parameters, no significant effects were detected under exposure to the field compared to placebo condition. Thus, under the given experimental conditions, autonomic control of heart rate was not affected by weak pulsed high frequency EMF, which was a conclusion others have also reached [Braune et al., 2002].

To re-investigate the influence of EMF of cellular phone GSM signals on human sleep EEG pattern of Mann and Röschke [1996], Wagner et al. [1998] recorded all-night polysomnographies of 24 healthy male subjects, both with and without exposure to a circular polarized EMF (900 MHz), pulsed with a frequency of 217 Hz, pulse width 577 μs, power flux density 0.2 W/m^2. Suppression of REM sleep, as well as a sleep inducing effect under field exposure, did not reach statistical significance, so that previous results indicating alterations of these sleep parameters could not be replicated. Spectral power analysis also did not reveal any alterations of the EEG rhythms during EMF exposure. The failure to confirm the previous results might be due to dose dependent effects of the EMF on the human sleep profile. In the first study [Mann and Röschke, 1996], a linear polarized field was emitted from an antenna approximately 40 cm from the head; in this experiment a similarly positioned antenna emitted a circular polarized field. The linear polarized field and uncontrolled external reflections might have caused enhanced local power density of the EMF [Bernardi et al., 1996]. Secondly, the second experiment's power flux density was 0.2 W/m^2, versus 0.5 W/m^2 in the previous experiment [Mann and Röschke, 1996]. Exact dosimetry is not available from the earlier study. Neither of these findings can be generalized to cellular phone technologies, since the dosimetry is poorly defined in the first experiment and the circularly polarized antenna in this study differs from handsets' antennas.

Hietanen et al. [2000] explored the influence of RF exposure on human brain function by accessing the EEG activity of 19 volunteers exposed to cell phone frequencies. Ten of the subjects were men (28–48 years of age) and nine were women (32–57 years of age). The sources of exposure were five different cellular phones (analogue and digital models) operating at a frequency of 900 or 1800 MHz. The EEG activity was recorded in an awake, closed-eyes situation. Six 30 min experiments, including one sham exposure, were made for each subject. The duration of a real exposure phase was 20 min. Exposure to one of the phones caused a statistically significant change in the absolute δ power band of the EEG recording. However, no difference was seen in the relative power of the same band, and no changes occurred during exposure to other phones at any frequency band. This study suggests that exposure to RF fields emitted by cellular phones has no abnormal effects on human EEG activity. As the authors point out, the observed difference in one parameter was probably caused by ''statistical chance'' [Hietanen et al., 2000].

In the EEG studies discussed next, the effects of EMF on various conscious functions were investigated. Eulitz et al. [1998] studied the interaction of cell phone pulsed MW exposure within the human brain. Subjects were 13 healthy males 21–27 years old. The MP was mounted on the head such that the base of the antenna was positioned over the left posterior temporal region. Their investigations were single blind. They showed that the EMF alter distinct aspects of the brain's electrical response to acoustic stimuli. Aspects of the induced but not evoked brain activity during pulsed EMF (PEMF) exposures were different from those not exposed. This effect appears in higher frequency bands when subjects process task relevant target stimuli, but was not present for irrelevant standard stimuli. As the induced brain activity in higher frequency bands has been proposed to be a correlate of coherent high frequency neuronal activity, PEMF exposure may provide a means to systematically alter the pattern fluctuations in neural mass activity.

Freude et al. [1998] found a significant effect on slow brain potentials at central and temporo-parieto-occipital regions during exposure to cell phone emissions. The influence of EMF emitted by a cellular phone positioned at the left ear, on preparatory slow brain potentials (SP) was studied in two different tasks: in the first, healthy male human subjects had to perform simple self-paced finger movements to elicit a Bereitschaftspotential (BP); in the second, they performed a complex and cognitive demanding visual monitoring task (VMT). The subjects were 16 healthy right-handed males, 21–26 years. Both tasks were performed with and without EMF exposure in counterbalanced order. Whereas subjects' performance did not differ between the EMF exposure conditions, SP parameters were influenced by EMF in the VMT. EMF exposure affected a significant decrease of SPs at central and temporo-parieto–occipital brain regions, but not at the frontal one. In the simple finger movement task, EMF did not affect the BP.

In another cell phone study conducted by Freude et al. [2000], subjects were 20 healthy right-handed males, 21–30 years of age, exposed between 9 am–12 am. The influence of EMF (916.2 MHz 217 Hz pulse frequency, pulse width 577 μs radiated aerial power, 2.8 W/kg SAR, emitted by cellular telephones near the left ear) on preparatory SP was studied in two

experiments, about 6 months apart. In the first experiment, a significant decrease of SP was found during exposure to EMF in a complex VMT. The effect was replicated in the second experiment with 19 male subjects. In addition to the VMT, EMF effects on SP were analyzed in two further, less demanding tasks: a simple finger movement task to elicit a BP and a two stimulus task to elicit a contingent negative variation (CNV). In comparison to the VMT, no significant main EMF effects were found in BP and CNV tasks. The results accounted for a selective EMF effect on particular aspects of human information processing, but did not indicate any influence on human performance, well being, and health.

The neurophysiological basis for the slow potentials is very speculative, but appears to be a self-regulatory mechanism in the brain to prevent the possibility of over reacting beyond control, as exhibited in epileptic seizures. SPs are possibly a recording of the tuning of cortical excitability, realized by control of depolarization in apical dendrites of cortical cells receiving input from thalamocortical neurons relaying motor excitation [Birbaumer et al., 1990]. This is a very difficult paradigm for interpreting any RF effects on memory or learning tasks because the behaviors tested may not be directly related to the recording of SPs. Also, there are many uncontrolled intervening variables. These include mood and motivation, which are reported to have a large influence on the size of the slow wave potential [Birbaumer et al., 1990].

Thimonier et al. [1997] looked for an effect of GSM 900 MHz exposure on evoked auditory brainstem responses (ABR) (160–1500 Hz) in 20 young subjects, 20–30 years of age. ABRs are action potentials emitted by different neurons in the brainstem that conduct the nervous message from the inner ear to the cortex when the external ear is stimulated, in this instance by a 100 μs short noise click at 80 dB intensity. Under the conditions of their protocol, a 1 h exposure to MP RF had no effect on ABRs (four peaks defined: Auditory nerve, Cochlear nuclei, Superior olivary complex, Inferior colliculus) or on distortion products of otoemission recordings.

Krause et al. [2000a] studied the effects of EMF emitted by cellular phones on the Event Related Synchronization (ERS), an increase in band power, and Event Related Desynchronization (ERD), a decrease in band power of the 4–6, 6–8, 8–10, and 10–12 Hz EEG frequency bands, in normal subjects performing an auditory memory task. All subjects performed the memory task, both with and without exposure to a digital 902 MHz EMF at the right ear, in counterbalanced order. The exposure to EMF significantly increased EEG power in the 8–10 Hz frequency band only. Nonetheless, in post hoc analysis the presence of EMF altered the ERD/ERS responses in all studied frequency bands as a function of time and memory task (encoding vs. retrieval). The numerous post hoc comparisons contravened statistical rules. Their results suggest that the exposure to EMF does not alter the resting EEG per se, but modifies the brain responses significantly during a memory task.

Krause et al. [2000b] tested 24 right-handed young adults in a visual sequential letter 'N-back' task under similar exposure conditions. There were no main effects of EMF at any frequency band in the visual N-back tasks. Nonetheless, the post hoc analysis showed an EMF effect at 6–8 Hz, most prominent in the left hemisphere, and at 8–10 Hz there were enhancements of desynchrony in the 0 and 1 back EMF condition and enhancement of the synchrony in the 2 back condition. There was a selective recording of the EEG bands, leaving out the synchronous γ bands. Recent research has called into scientific doubt the concept of desynchrony as a valid EEG classification. The term ''desynchronized'' for the activated states of waking and REM has been rendered obsolete by the discovery of highly synchronized γ frequency (30–80 Hz) activity in these states [Hobson and Pace-Schott, 2002].

Jech et al. [2001] examined the effects of the MP EMF on EEG and event-related potentials (ERP). Narcolepsy-cataplexy patients ($n = 22$), mean age 48 years, supine in a dimmed room, were exposed or sham exposed for 45 min to the mobile telephone (MP, Motorola d520, 900 MHz, 217 Hz, pulse width 577 μs, 2.8 Hz, 0.25 W SAR 0.06 W/kg) placed close to the right ear in a double blind study. There were no changes of the EEG recorded after the MP exposure. A subgroup of 17 patients was studied on visual ERP recorded during the MP exposure. Each patient was instructed to strike a key whenever rare target stimuli were presented. The exposure enhanced the positivity of the ERP endogenous complex in response to target stimuli in the right hemifield of the screen ($P < .01$). The reaction time was shortened by 20 ms in response to all target stimuli ($P < .05$). The EMF of MP may suppress the excessive sleepiness and improve performance while solving a monotonous cognitive task requiring sustained attention and vigilance.

EEG summary. In a recent study, Hamblin and Wood [2002] reviewed 14 articles that studied the effects of GSM MP RF energy on human brain activity and sleep variables. Overall, they point out that outcomes of the various studies have been inconsistent and comparison between individual studies is difficult. Several studies

noted the enhanced α band power observed in both human and some animal studies. Since the largest amount (50–60%) of sleep time in young adults is spent in stage II NREM sleep [Kandel et al., 2000] and is characterized by distinctive sleep spindles (α: 12–14 Hz) and K complex waveforms [Hobson and Pace-Schott, 2002], effects reported on sleep EEG are more likely to involve NREM α waves, compared to other bands, as they do in these EEG experiments on young subjects.

Other studies have shown that enhanced brain electrical activity in the α band is consistent with results of extremely low frequency (ELF) studies where performance deficits are reported to occur. However, these studies are not comparable and appear methodologically flawed; other laboratories have found no such effects. The issue of ELF fields associated with the MP power supply has been brought up before [Anderson and Pedersen, 1997; Linde and Mild, 1997]. Whether ELF fields produced by modulation of battery power and current associated with the RF signal could have a role in the outcome of some studies is not understood. In other studies, more complex cognitive tasks showed improvement of performance with exposure; and since these changes are reported for both modulated and unmodulated carrier signals, the role of ELF generated fields in producing the effects seems weak. There seems to be no correlation with site of exposure and brain regions likely involved in the effects.

Within laboratories hypnotic effects have not been replicated [Mann/Röschke group and Kuster/Borbély group], and Mann and Röschke's [1996] EEG effects on sleep frequency bands were not replicated [Wagner et al., 1998]. Between laboratories there is disagreement about EMF effects on the EEG of REM, NREM and awake states and during various types of tasks. Serious deficiencies in EEG human studies using EMF exposure include poor dosimetry. The placing of the signal in relation to the head has not been defined in stereotaxic, three dimensional coordinates. Also, the SAR distribution in the head has not been measured for the most part. Without these dosimetrically precise details of SAR at an neuroanatomical resolution of 2 mm^3 in the brain, it is impossible to correlate local changes in EEG from any experiment to the specific neuroanatomy of the brain and its associated neurophysiology when asleep, awake, or during cognitive behaviors [Van de Kamer and Lagendijk, 2002]. It is also impossible to compare results across experiments and between different laboratories in any meaningful way. And finally, without these exposure details it is impossible to replicate these experiments to validate the results in other laboratories. Most studies test only one dose with poor dosimetric controls and poor traceability. Possible interference and reflection of RF need to be assessed in exposure setups. Heat can induce sleep and changes in the EEG and could account for positive findings. As a result no conclusions can be drawn from the present EMF–EEG research.

If EMF–EEG research continues the simplest of paradigms, and traceable dosimetry must be considered. The relation of the antenna to the brain must be defined in stereotaxic coordinates and the SAR fully mapped in the brain experimentally and numerically. The exposure should be relevant to the WHO health criteria for evaluation of the safety on mobile telephones. The exposure paradigm must take into account and control interference and reflection of EMF within the test setting. It is recommended that several laboratories simultaneously replicate an identical paradigm, including time course and dose effect features. Special attention should be taken to avoid complex cognitive studies, since at present there is no assurance that the tests measure what they purport to measure, their anatomical correlates are uncertain, and their relationship to an EEG recording is very speculative. It remains a challenge to separate the effect of direct RF fields and the effect due to induced RF current brought into the head by the conductive leads.

Cognitive Studies

MW heating is known to affect memory and learning [Saunders et al., 1991]. At 2 GHz, exposure is more superficial, with RF energy absorbed by skin rather than deeper tissues, compared to the lower MW frequencies of 900 and 450 MHz [see Adair et al., 1999, 2001]. These frequencies are used by current mobile communication systems. Exposures in primates to frequencies between 225 MHz and 5.8 GHz for 1 h have been reported to result in significant decrements in performance of operant tasks [see de Lorge, 1983, 1984]. Threshold SARs were estimated to be 2.5 W/kg at 225 MHz (near body resonance) and 4–5 W/kg at the higher frequencies; however, colonic temperature rose in all cases by about 1 °C. The lowest SAR threshold for learning effects was found during exposure to more deeply penetrating fields at the lower frequency (225 MHz) [Saunders et al., 1991]. Exposure associated changes in cognition are summarized in Table 2.

Working memory. "Learning is the process by which we acquire knowledge about the world, while memory is the process by which that knowledge is encoded, consolidated, stored, and later retrieved .... Many important behaviors are learned .... Molecular mech-

TABLE 2. Effects of RF Exposure on Cognitive Performance

EMF effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
They calculated a maximum rise in brain temperature of 0.11 °C for an antenna with an average emitted power of 0.25 W, the maximum value in common mobile phones, and indefinite exposure	Human bioheat head model	Max 0.91 W/kg for 10 g	916		0.25 W	Indefinite exposure	Van Leeuwen et al. [1999]
There was evidence of a significant increase with the analogue but not with the digital simulation, in choice reaction time only. No effects on memory	Humans		915 and CW	217 Hz pulsed; 12.5% duty cycle	1 W mean power	25–30 min	Preece et al. [1999]
Subjective sensations of warmth around the ear. No effect on memory	Humans		Sweden 900 NMT	GSM		Normal use	Oftedal et al. [2000]
No effect on 9 tasks and 11 comparisons including choice reaction tasks measuring various stages of visual object or word recognition. Facilitatory effect on tasks requiring attention and manipulation of information in working memory	Humans		GSM 902	217 Hz		About 1 h, left ear	Koivisto et al. [2000a]
Memory load was varied from 0 to 3 items in an N-back test. Significantly speeded up response times on 3 items (on increased memory load)	Humans		GSM 902	217 Hz, GSM		30 min, left ear	Koivisto et al. [2000b]
No subjective symptoms in humans	Humans		902	217 Hz GSM		30–60 min	Koivisto et al. [2001]
902 MHz mobile phone exposure had no effect on performance of nine human cognitive tasks: a replication of Koivisto et al. [2000a] in Finland and Sweden	Humans: 32 males 32 females	0.88 W/kg aveover 10 g	902	GSM		65 min, left ear	Haarala et al. [2003]
On three measures of attention mobile phone users performed significantly better than controls on one test (Trail making)	72 Humans 16 years		Mobiles Hong Kong	GSM		Median 3712.5 min of use	Lee et al. [2001]
Significant effects were found for digit span forward, spatial span and serial subtraction tasks, 3 of 6 tests for exposed versus unexposed conditions	38 Humansage 21 years ave		900			30 min, left ear	Edelstyn and Oldershaw [2002]
Operant task: threshold for impaired performance 2.5 W/kg (at 225 MHz) 4–5 W/kg (at 1.3 and 5.8 GHz) whole body exposure, accompanied by a raised in core body temperature of 1 °C	Rhesus monkey		A: 225 CW; B: 1300 pulsed; C: 5800	A: none; B: 3 μs pulses 370 pps; C: 0.5 μs or 2 μs pulses 662 pps			de Lorge [1984]
Dosimetry paper for the same average incident power density, the average SARs in the heads of rats were about two times higher in the circular waveguide than for other exposures	Rats		2450 CW		1 mW/cm^2		Chou et al., [1985a]

No overall effect for 20 min exposure but more errors each day in a 12 arm radial maze at 45 min exposure	Rats	Ave whole body 0.6	2450	2 μs pulses, 500 pps	1 mW/cm^2 but high peak power	20 min/day and 45 min/day exposure for 10 days	Lai et al. [1989b]
Deficit in spatial "working memory" function reversed by pre-treatment with physostigmine or naltrexone, whereas pre-treatment with the naloxone methiodide showed no reversal of effect	Rats	Ave whole body 0.6	2450	2 μs pulses, 500 pps	1 mW/cm^2 but high peak power	45 min exposure	Lai et al. [1994]
Impaired performance at 1 °C rise in body and brain temperature (>9 W/kg) whole body exposure	Rats	0.1–10 W/kg	600 (CW)			20 min	Mickley et al. [1994]
These results show that acute exposure to pulsed microwaves (PW) caused a deficit in the spatial "reference" memory in the rat	Rats	1.2 W/kg	2450	Pulsed width 2 μs, 500 pulses/s	Average power density 2 mW/cm^2	For 1 h in a circular wave guide system	Wang and Lai [2000]
Low level exposure to pulsed 900 MHz microwave exposure does not cause deficits in the performance of a spatial learning task in mice	Mice	Whole body 0.05 W/kg	900	Pulsed at 217 Hz		45 min/day for 10 days	Sienkiewicz et al. [2000]
Exposure decreased response latency and task accuracy and enhanced cellular excitation recordings of firing rates from single neurons	Rats	In the brain of 1.32 W/kg	900	GSM		30 min	Thuroczy et al. [1994]
No deficits in spatial learning after "head only" exposure of rats to GSM electromagnetic fields in the two spatial learning tasks	Rats	1 or 3.5 W/kg	900	GSM modulation at 217 Hz, 1/8 duty factor		45 min over 10–14 days	Dubreuil et al. [2002]
These results suggest that low intensity RF fields can modulate the excitability of hippocampal tissue in vitro in the absence of gross thermal effects	Rat hippocampal slice	0.0016–0.0044 W/kg in the slices	700 CW		25.2–71.0 V/m	5–15 min exposure	Tattersall et al. [2001]
The experiments gave no indication of any specific biological action of a brief RF exposure, even at peak SAR as high as 330 kW/g	Rat hippocampal slice	Peak 10 W/kg up to 330 kW/g	9300	Pulse width 0.5–2.0 μs; 2 μs (0.5 Hz repetition rate) or 0.5 μs (2 Hz repetition rate)		For 2 min	Pakhomov et al. [2003]
No significant effects on the reference memory performance of rats were found due to RF exposure where the average SAR within the brain was 7.4 W/kg and the whole body average SAR was 1.4 W/kg	Rats	I: Brain (B) 7.4 W/kg and whole body (WB) 1.4 W/kg; II: B 25 W/kg and WB 4.5 W/kg	1439	PDC (Japan)		I: 1 h/day for 4 days; II: 45 min/day for 4 days	Yamaguchi et al. [2003]
The results of analyses of error rates included no significant "exposure" effect, no significant "drug" effect and no significant interactions between those two factors	S–D rats	0.6 W/kg	2450	Pulsed		45 min per day for 10 days	Cobb et al. [2003];Lai et al. [1994] replication

anisms of memory storage are highly conserved throughout evolution, and complex forms of learning and memory depend on many of the same molecular mechanisms used in the simplest forms. . . . These molecular mechanisms contribute to our individuality by changing the connectivity of neurons in our brains'' [Kandel et al., 2000].

Working memory or short term memory has four component systems: an attention control system, possibly located in the prefrontal cortex, actively focuses perception on specific events. The attention control system has a limited capacity of less than a dozen items. The attention control system regulates the information flow to two rehearsal systems, the articulatory loop for language words and numbers, e.g., rehearsal of telephone numbers, and the visuospatial sketchpad for vision and action. The extrastriate cortex is important for rehearsal of visual imagery and the parietal cortex, for rehearsal of spatial imagery. And the medial temporal lobe is essential for Hebb's mechanism of encoding working memory for explicit knowledge. Memory consolidation involves three processes: (1) gene expression, (2) new protein synthesis, and (3) growth or pruning of synaptic connections.

Learning and memory in humans. Van Leeuwen et al. [1999], using a realistic head model, evaluated the 3D temperature rise induced by a 915 MHz MP antenna with an average emitted power of 0.25 W, which is the maximum value in common phones an indefinite exposure time. This was done both numerically, with an FDTD model to predict the SAR distribution, and with a thermal model describing bioheat transfer both by conduction and by blood flow. They calculated a maximum rise in brain temperature of 0.11 °C. The power distributions were characterized by a maximum averaged SAR over an arbitrarily shaped 10 g volume of approximately 1.6 W/kg. This is the first temperature assessment during MW exposure on a model head that simulates heat transfer by blood flow. They suggest the temperature rise from the 915 MHz MP at maximum power in the brain is well below the 1 °C rise in temperature where learning effects are known to occur.

Preece et al. [1999] examined whether a simulated MP transmission at 915 MHz has an effect on cognitive function in man. Thirty-six subjects, 21–60 years of age (two were left handed) in two groups, had three test sessions in a randomized three way cross-over design. Exposure was from a 915 MHz antenna mounted on a simulated analogue phone. A sine wave, or GSM signal modulated at 217 Hz with 12.5% duty cycle, 1 W average power, was directed to the left region of their head behind the ear, while subjects undertook a series of cognitive tests lasting ∼25–30 min. There were no changes in word, number, or picture recall, or in spatial memory. There was a significant increase in choice reaction time with the analogue but not with the digital simulation exposure. This effect was within normal variance since the SEM is ±40 ms for choice reaction time, much larger than the significant effect of 14 ms reported here on the analogue phone at 1 W power [Woodruff-Pak et al., 1999]. Analogue MPs have a power class specification of 0.6 W; this simulated phone (1 W) is well above the commercial approved power level. SAR measurements are not available. These results cannot be applied to either a GSM phone or an analogue phone, since neither simulated phone was accurately assessed for power emission or RF exposure levels.

People in Norway and Sweden have made subjective reports of headaches, fatigue, and other symptoms experienced in connection with the use of a MP. Oftedal et al. [2000] carried out a cross-sectional epidemiological study among 17 000 people, all using a MP in their job. Thirty-one percent of the respondents in Norway and 13% of those in Sweden had experienced at least one symptom in connection with MP use. These people reported an awareness of subjective sensations of warmth around the ear, but no awareness of effects on memory.

Koivisto et al. [2000a] examined possible influences of a 902 MHz EMF emitted by cellular phones on cognitive functioning in 48 healthy humans. A battery of 12 reaction time tasks was performed twice by each participant in a counterbalanced order, once with and once without the exposure to the field, over about 1 h. The results showed that the exposure to EMF emitted from a MP placed on the left ear speeded up response times in simple reaction time, while vigilance tasks and the cognitive time needed in a mental arithmetic task were decreased. They suggested that a 902 MHz GSM phone gave a slight improvement in cognitive processing in three out of fourteen cognitive tasks: simple reaction time, vigilance and cognitive time in mental arithmetic.

This study fails to meet many of the IEEE C95.1-1999 criteria for good research, which at minimum includes proper dosimetry [see ANSI/IEEE C95.1-1999, 1999, Sections 6.2–6.4]. The untraceable dosimetry and nonvalidated cognitive tests weaken the scientific value of the article. The multiple comparisons exaggerate the chances for a significant effect. The study did not measure the actual power emitted by the phone or the power absorbed by the head. There is no way of accurately knowing the position of the phone since the researchers failed to measure the 3D (stereotaxic) position of the phone in relation to the brain. There was no positive control, which is a re-

quirement of good human acute studies. Neither the possible cognitive behaviors affected in the brain nor the heat mechanisms postulated are supported by existing evidence [Pennes, 1948; Foster and Erdreich, 1999; Van Leeuwen et al., 1999; Wang and Fujiwara, 1999].

In a replication and extension of Koivisto et al. [2000a] with methodological improvements, Haarala et al. [2003] had subjects perform a battery of nine cognitive tasks, including six tasks repeated from Koivisto et al. [2000a] twice in two independent laboratories in Sweden and Finland. Improvements included a double blind study, multicenter testing with order of subjects counter balanced across subjects and gender, measurements of the SAR of the phones with the SPEAG's Dosimetric Assessment System 3 (DASY3, Schmid & Partner Engineering AG, Zurich, Switzerland), measurements of the temperature with a type K thermocouple sensor and a TES-1300 thermometer (TES Electrical Electronic Corp., Taipei, Taiwan), and statistical analyses performed using SPSS software (SPSS, Inc., Chicago, IL). There were no statistically significant differences in performance between genders or laboratories (without the Bonferroni correction). Although the reaction times and the accuracy of answers were very similar to the previous study, the previous results were not replicated. The results employing a better controlled study design, replicated in two independent laboratories, indicate the GSM MPs do not have an effect on cognitive functioning.

In the time between the publication of Koivisto et al. [2000a] and the above replication [Haarala et al., 2003], two studies from other laboratories were published measuring effects of MP RF exposure on attention. Lee et al. [2001] examined the effect of exposure to the EMF emitted by MPs on human attention. Three measures of attention were administered to 72 teenagers, 37 of whom were MP users. The results showed that the MP users performed better on one of the three measures of attention than did the nonusers. Design flaws include no SAR measurements and the failure to randomize order of presentation and exposure. Sampling bias was also indicted as factor. Edelstyn and Oldershaw [2002] carried out a study to investigate the effects of acute MP exposure on six tasks purported to test processing speed within the human attentional system. Thirty-eight healthy volunteers were randomly assigned to either an experimental group that was exposed to a connected MP or a control group in which the 900 MHz MP was switched off. They report significant differences between the two groups after 5 min on two tests of attentional capacity (digit span forwards and spatial span backwards) and one of processing speed (serial subtraction). No SAR measurements were carried out and the study was not double blind.

To test their hypothesis that exposure to the EMF emitted by cellular phones may have a facilitatory effect on brain functioning, especially in tasks requiring attention and manipulation of information in working memory, Koivisto et al. [2000b] studied the influence of pulsed RF fields of digital GSM MPs (902 MHz, 217 Hz pulse modulation) on working memory. Subjects were 48 healthy volunteers, 18–34 years old. They were exposed to the GSM phone for 30 min while doing N-back memory tasks under single blind conditions. Memory load was varied from 0 to 3 items in an N-back test. Each subject was tested twice within a single session, with and without the GSM exposure. The ANOVA main effect for RF or type was not significant. But on further analysis it was found the RF field speeded up response times when the memory load was three items (increased memory load) but showed no effects with lower loads. Their results suggest that RF fields have a measurable effect on human cognitive performance and encourage further studies on the interactions of RF fields with brain function. But similar objections are relevant to this study as to their previous study [Koivisto et al., 2000a].

Koivisto et al. [2001] in their third study tested the influence of pulsed RF fields of digital GSM mobile phones (as above) on subjective symptoms or sensations in healthy subjects in two single blind experiments. The duration of the RF exposure was about 60 min in Experiment 1 and 30 min in Experiment 2. The results did not reveal any differences between exposure and nonexposure conditions, suggesting that a 30–60 min exposure to this RF field does not produce subjective symptoms in humans. Thus the effect on cognitive behaviors in their two previous experiments (above) would not be confounded by subjective sensations from the mobile phone exposure [see Hietanen et al., 2002].

Conclusion on human cognitive studies. The human acute studies' positive results on learning and memory from MP exposure are put into perspective by the failed replication of Koivisto et al. [2000a] in a subsequent study with improved methodology by Haarala et al. [2003]. In most of the previous studies, the experimenters had been aware of the EMF conditions. Although there exist several reports of speeding up of reaction times due to EMF in tasks requiring attention and short term memory, the effects are only in a small number of tasks used; most of the tasks have shown no effect. Also, because the authors failed to use the appropriate statistical corrections for the multiple comparisons (i.e., Bonferroni), the statistical chances

for significant effects were exaggerated. The many versions of attentional tasks the above experimenters have used are testimony to their large variability in measurement and the poor understanding of these attributes. In most cases, the researchers have not validated the items in their test battery, and as a result it is not possible to know whether they measured various aspects of attention that they claimed and whether they measured them reliably. It is somewhat reassuring to note that the reaction times in Koivisto et al. [2000a] and in Haarala et al. [2003] are similar. This fact, together with the lack of significant differences between the two independent laboratories in the Haarala replication study, may indicate their tasks are reliably measuring stable attributes and that their results reliably indicate no significant effect of MP exposure on these measured attributes of cognition. Further well-controlled studies are required to validate conclusions on whether MP exposures affect cognition especially in the long term.

Learning and memory in animals. In the decade 1970–1980, researchers investigated RF effects on operant tasks in rats and concluded that a raised core body temperature of about 1 °C accompanied changes in performance [D'Andrea et al., 1976; Mitchell et al., 1977; Sanza and de Lorge, 1977; de Lorge and Ezell, 1980; Schrot et al., 1980]. Changes in primates' operant behavior appeared at higher threshold RF exposures than rats because the rhesus monkey absorbed higher SAR before core body temperature rose 1 °C [Scholl and Allen, 1979; de Lorge, 1984].

Spatial memory: hippocampus. Later animal studies [1990–2002] investigated RF effects on working memory tasks, using the maze paradigm primarily in rats. Spatial working memory involves the hippocampus. The hippocampus contains a cognitive map of the spatial environment in which an animal moves [O'Keefe and Dostrovsky, 1971]. The location of an animal in a particular space is encoded in the firing pattern of individual pyramidal cells, the very cells that undergo long term potentiation when their afferent pathways are stimulated electrically. Long term potentiation is important for the formation and maintenance of place fields and defects in long term potentiation interfere with spatial memory.

Lai et al. [1994] reported that after 45 min of exposure to pulsed 2450 MHz microwaves, 2 μs pulses, 500 pps, 1 mW/cm^2, average whole body SAR 0.6 W/kg, rats showed retarded learning while performing in the 12 arm radial maze to obtain food rewards, indicating a deficit in spatial "working memory" function. This study used the well-characterized circular wave guide [Chou et al., 1984, 1985a] that results in exposure of the head two times higher than for other exposures. The behavioral deficit was reversed by pretreatment before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter systems in the brain may be involved in the MW induced spatial memory deficit. This paradigm has a high peak power that would result in the rats hearing auditory clicks during exposure [Chou et al., 1985b].

Using the circular water maze, Lai's group [Wang and Lai, 2000] trained rats in six sessions to locate a submerged platform. Rats were exposed to pulsed 2450 MHz microwaves, pulse width 2 μs, 500 pulses/s, average power density 2 mW/cm^2, whole body average SAR 1.2 W/kg, for 1 h in a circular waveguide system immediately before each training session. One hour after the last training session, they were tested in a probe trial during which the platform was removed and the time spent in the quadrant of the maze where the platform had been located during the 1 min trial was scored. Three groups of animals, MW exposed, sham exposed, and cage controls, were studied. They concluded that MW exposed rats were slower than sham exposed and cage controls in learning to locate the platform. However, the calculated energy in the pulse (2.4 mJ/kg peak, peak SAR 2400 W/kg) would result in hearing auditory clicks [Chou et al., 1985b]. Lai et al. [1994] and Wang and Lai [2000] may have statistical problems, since the exposed and sham animals exhibited no apparent interaction between testing days and treatment.

Mickley et al. [1994] found that acute exposure to 600 MHz fields at SARs up to 10 W/kg for 20 min produced deficits in working memory in rats when the temperature in brain and rectum was raised by 1 °C.

Dubreuil et al. [2002] used two behavioral tasks that are well established paradigms to test performance deficits in spatial learning after EM exposure: the 8 arm radial maze elimination task and a spatial navigation task in an open field arena (dry land version of the Morris water maze). They were the first to use a head only exposure system emitting a 900 MHz GSM EM field, pulsed at 217 Hz. The performances of rats exposed for 45 min to a 900 MHz field (1 and 3.5 W/kg) were compared to those of sham exposed and cage control rats. There were no differences among exposed, sham, and cage control rats in the two spatial learning tasks.

Cobb et al. [2003] reexamined the possibility for changes in "working" memory in rats following

whole body exposure to MW exposure [Lai et al., 1994]. For each of 10 days, they exposed rats within circular polarized waveguides for 45 min to 2450 MHz fields at whole body SARs of 0.6 W/kg, 2 μs pulses, 500 pps, followed by testing in a 12 arm radial maze. Rats received a preexposure injection of one of three psychoactive compounds or saline, to examine whether these compounds would interact with MW exposure to affect performance in the maze. Maze performance was evaluated using ''error rates,'' i.e., reentry into arms already visited, and ''time to criterion.'' ANOVA of error rates included no significant ''exposure'' effect, no significant ''drug'' effect, and no significant interactions between those two factors. There was a significant difference in ''test days,'' as expected with repeated test trial days; this indicates that learning was accomplished. ANOVA of ''time to criterion'' data included no significant ''exposure'' effect, a significant ''drug'' effect, a significant ''test day'' effect, and a significant interaction between drug and test day factors. Post hoc analyses of the ''drug'' factor revealed that rats pretreated with either of the two centrally acting drugs, physostigmine or naltrexone hydrochloride, took significantly longer to complete the maze task than those pretreated with either saline or the peripherally acting drug naloxone methiodide. The authors conclude there is no evidence that exposure to the level of MW exposure examined here causes decrements in the ability of rats to learn this spatial memory task.

The only mouse maze study to investigate if short term memory loss or other cognitive effects are associated with the use of mobile cellular telephones was undertaken by Sienkiewicz et al. [2000]. The effect of repeated, acute exposure to low intensity 900 MHz RF pulsed at 217 Hz was explored using an appetitively motivated spatial learning and working memory task. Adult male C57BL/6J mice were exposed under far field conditions in a GTEM cell for 45 min each day for 10 days at an average whole body SAR of 0.05 W/kg. Their performance in an 8 arm radial maze was tested immediately following exposure or after a delay of 15 or 30 min. No significant field dependent effects on performance were observed in choice accuracy or in total times to complete the task across the experiment.

A recent study by Yamaguchi et al. [2003] sought to clarify the effects of cellular phone exposure on learning and memory by studying reversal learning in a food rewarded T maze, in which rats learned the location of food (right or left) by using environmental cues. Rats were exposed for either 1 h daily for 4 days or for 4 weeks to a pulsed 1439 MHz TDMA signal in a carousel type exposure system. Average SAR in the brain was 7.5 W/kg, and the whole body average SAR was 1.7 W/kg. Other subjects were exposed at the brain average SAR of 25 W/kg and the whole body average SAR of 5.7 W/kg for 45 min daily for 4 days. The rats exposed to the higher brain SAR of 25 W/kg showed statistically significant decreases in the number of correct choices in the reversal task, compared to sham exposed or cage control animals. Only this group showed significant behavioral changes and a body temperature rise (∼2 °C). These results suggest that the exposure to TDMA signals from cellular phones does not affect the learning and memory processes when there are no thermal effects.

Hippocampal slices in vitro. Tattersall et al. [2001] used the hippocampal slice preparation for in vitro investigation of the effects of RF during hippocampal neuronal recording of population spikes. They recorded extracellular field potential responses in stratum pyramidal or stratum radiatum of the CA1 or CA3 regions. In the ''Results'' section, the recordings are described as ''effects of exposure to 700 MHz fields on the population spike amplitude in hippocampal slices.'' For the most part they did not distinguish CA1 from CA3 recordings in this study. Slices of rat hippocampus were exposed to 700 MHz continuous wave RF fields (25.2–71.0 V/m, 5–15 min exposure) in a stripline waveguide. At low field intensities, the predominant effect on the electrically evoked field potential in CA1 was a potentiation of the amplitude of the population spike by up to 20%, but higher intensity fields could produce either increases or decreases of up to 120 and 80%, respectively, in the amplitude of the population spike (PS). The effects of RF on the PS were variable, with decreases and increases in population spikes; and the most significant result was their variability, not their consistency. ''Due to the variability of the response to RF between slices, however, none of the field intensities produced a statistically significant effect in terms of mean change. There was, however, a significant increase in variability at 50.2 V/m (F test $P < .05$)'' [Tattersall et al., 2001].

To eliminate one possible RF induced artifact due to the metal stimulating electrode, they investigated the effect of RF exposure on spontaneous epileptiform activity induced in CA3 by 4-aminopyridine (50–100 μM). Perfusion with 4-aminopyrridine induced spontaneous synchronized bursts of activity in the CA3 region, which occurred at a frequency of 0.1–0.3 per second. Slices were exposed in the waveguide to 700 MHz RF fields at increasing field intensities up to 71 V/m for 5 min at each intensity. In four out of 11 slices tested, exposure produced a transient increase in the frequency of the bursting accompanied by a decrease in the amplitude of the bursts; this followed a lasting decrease in frequency that recovered slowly

when the field was turned off. Thus RF had an effect on less than half the slices during spontaneous epileptiform activity induced in CA3 by 4-aminopyridine [Tattersall et al., 2001].

Exposure to RF fields (50.0 V/m) was calculated post hoc to produce a SAR of between 0.0016 and 0.0044 W/kg in the slices. Measurements with a Luxtron fiber optic probe confirmed that there was no detectable temperature change (±0.1 °C) during a 15 min exposure to this field intensity. These results suggest that low intensity RF fields may modulate the excitability of hippocampal tissue in vitro in the absence of gross thermal effects. Imposed temperature changes of up to 1 °C failed to mimic the effects of RF exposure [Tattersall et al., 2001].

Since the dosimetry was calculated post hoc, another laboratory needs to verify the calculations and replicate the experimental results. The anesthetic halothane was used, and it is possible that the evoked potentials of CA3 and CA1 would be affected by this drug. The authors state that constant current stimuli (pulse duration 70 μs amplitude 100–300 μA) were delivered at intervals of 10–30 s to avoid the development of long term potentiation (LTP) or depression. Avoiding of development of LTPs may also be attributed to the halothane anesthesia. Experiments need to be done with rat hippocampi from unanesthetized rats to verify that there was no anesthetic effect. The authors state that afferent pathways were stimulated with a concentric bipolar stainless steel electrode placed in the stratum radiatum. RF pickup is a concern with a conducting electrode. The authors for the most part do not distinguish the CA1 from the CA3 recordings, but just report slice recordings. They make no anatomical maps to illustrate their recording sites. There are major differences in the electrophysiology and role in memory of the CA1 pyramidal cells and the CA3 pyramidal cells. This may confound their results [Tattersall et al., 2001].

The Mossy fiber terminals: long term potentiation (CA3). The mossy fiber terminals in CA3 release glutamate as a transmitter. The NMDA receptors of CA3 have only a minor role in synaptic plasticity. Long term potentiation depends on Ca^{2+} influx into the presynaptic cell (granule cell terminal) after the tetanus. The Ca^{2+} influx appears to activate Ca^{2+}/calmodulin dependent adenylyl cyclase, thereby increasing the level of cAMP and activating PKA in the presynaptic neuron, just as in the sensory neurons in Aplysia during associative learning. Mossy fiber long term potentiation can be regulated by a modulatory input from noradrenergic neurons that engage B-adrenergic receptors, which activate adenylyl cyclase, as does the serotonergic input of Aplysia. Long term potentiation in the mossy fiber pathway is nonassociative. The LTP does not require simultaneous firing in both the postsynaptic CA3 cell and presynaptic dentate cell to adequately depolarize the CA3 postsynaptic cell, a feature called ''nonassociativity.''

Schaffer collateral and perforant pathways: long term potentiation (CA1). Long term potentiation in the Schaffer collateral is associative. A similar set of mechanisms is responsible for long term potentiation in the Schaffer collateral and perforant pathways. The Schaffer pathway connects the pyramidal cells of CA3 region to those of the CA1 region. The Schaffer collateral fiber terminals release glutamate as a transmitter; but long term potentiation in the Schaffer collateral pathway requires activation of the NMDA-type receptor. Long term potentiation in CA1 cells has two NMDA characteristic features that distinguish it from the LTP of the mossy fibers.

The Schaffer collateral pathway requires simultaneous firing in both the postsynaptic CA1 and presynaptic CA3 cells to adequately depolarize the postsynaptic CA1 cell, a feature called associativity. To initiate the Ca^{2+} influx into the postsynaptic cell, a strong presynaptic input sufficient to fire the postsynaptic cell is required. The finding that the LTP in the Schaffer collateral pathway requires simultaneous firing in both the presynaptic and postsynaptic neurons provides direct evidence of Hebb's rule [Kandel et al., 2000]. Hebb's rule provides a way to explain how a neuron can ''learn'' to produce a desired output from given inputs.

It would be appropriate to investigate memory effects by inducing LTP in the CA1 pyramidal cells and recording at CA1 to test for effects of RF on LTP associated with spatial memory.

Conclusions on animal learning and memory studies. Two questions arise: Can we extrapolate the consistent results showing no RF effects on spatial memory in rats and mice in the radial arm maze [Sienkiewicz et al., 2000; Dubreuil et al., 2002; Cobb et al., 2003] to other types of learning and also to humans? The answers can be found from the molecular mechanisms of memory.

Molecular units for learning. The changes in synaptic efficacy that we have encountered in studies of both implicit and explicit forms of storage are explained in three key points in the neurobiology of learning. First, simpler forms of plasticity may represent elements of more complex forms. Second, the molecular mechanisms of elementary forms of associative memory

storage used in both implicit and explicit learning are similar. Explicit memory in mammals involves long term potentiation in the hippocampus. The plasticity of neuronal function seems to derive from the ability of proteins such as adenylyl cyclase and the NMDA receptor to respond conjointly to two independent signals. Third, despite differences in behavioral logic in the neural systems recruited for the task, implicit and explicit memory storage seem to use elements of a common genetic switch, involving cAMP dependent protein kinase, MAP kinase, and CREB to convert labile short term memory into long term memory [Kandel et al., 2000].

The answer is that we appear to be able to extrapolate spatial memory effects from animals to humans; indeed spatial memory has been researched in taxi drivers and the spatial processing is located in the human hippocampus [Maguire et al., 1996, 1998]. And the molecular mechanisms are similar for explicit and implicit memory. Thus we can extrapolate to other forms of learning as well in other parts of the brain. It is reasonable to consider the RF completely penetrated the rat and mouse hippocampi as the rat and mouse brains are tiny in comparison to human's. If RF at several doses, both below and well above RF guideline limits, did not affect spatial memory in rats and mice, then based on the understanding of the neurobiology of the molecular mechanisms of memory, RF within the current guidelines is unlikely to affect human memory of any type in any structure of the human brain. Further research is underway to verify our current understanding of the interaction of RF with memory and learning.

Morphology

Early studies of morphological effects on animals were conducted in the Eastern European countries. These studies reported that pulsed MW exposure has more marked effects than CW and that chronic exposure is more damaging than acute exposure. At high exposure levels, severe vascular disorders, such as edema and hemorrhages in the brain, were prominent. These changes were similar for SARs above 2 W/kg, and the degree of effect was greater at higher exposure levels [Gordon et al., 1974; Kalada et al., 1974].

Webber et al. [1980] reported morphological changes in mouse neuroblastoma cells, grown in vitro and exposed to MW (2.7 GHz, 1.7–3.9 kV/cm, 1 μs pulses at 330 pulses/s) and to heat by raising solution temperature. The most striking damage occurred in the form of breaks in the cellular and mitochondrial membranes. Parts of the cell membrane were expelled and appeared as membrane bound sacs outside the cell surface. Cristae lost their normal pattern and formed myelinated figures inside mitochondria. Webber et al. [1980] suggested that these effects might be of a nonthermal nature because the results of MW exposure are different from that of solution heating. However, it is difficult to compare these, since the rate of heating cannot be simulated for pulsed MW heating. Articles discussing morphological changes are summarized in Table 3.

Albert and DeSantis [1975] showed cellular alterations in hypothalamic and subthalamic regions near the center of Chinese hamsters' brains exposed to 2.45 GHz at 50 mW/cm^2 (SAR ~15 W/kg). Vacuolation of neurons but not glia was also seen in the hypothalamic region of animals exposed to a SAR of 7.5 W/kg. Albert et al. [1981a] studied the effects of 46 mW/cm^2 (SAR 2.8 W/kg) at 100 MHz and 10 mW/cm^2 (SAR 2 W/kg) at 2.45 GHz during exposures of cerebellar Purkinje cells inside developing rat brains. Exposure to both frequencies had similar significant and irreversible decreases of Purkinje cells in rats irradiated either during their fetal or their fetal and early postnatal life. Significant decreases in the relative number of Purkinje cells were apparent in animals exposed postnatally and euthanized immediately after exposure. However, restoration apparently occurred after 40 days. Albert and Sherif [1988] summarized this work. In another study, Albert et al. [1981b] exposed pregnant squirrel monkeys to 2.45 GHz microwaves (SAR 3.4 W/kg, 10 mW/cm^2) for 3 h/day, 5 days/week during the offspring's first 9.5 months and studied the effects on the density of Purkinje cells in the offsprings' cerebellar uvula. There was no significant effect on monkey Purkinje cells.

The monkey data are different from the rat data. However, the two studies are not truly comparable because too many variables are different. For example, Albert et al. [1981b] point out that differences in the anatomical structure of the head and exposure conditions (free field vs. multipath) could contribute to the difference in results. Also, 2450 MHz may be closer to the resonant frequency of the rat, and the depth of penetration of RF energy may be important. Too, the structure of the brain in each species presents different exposure configurations. In the rat, the cerebellum is exposed in the dorsal and posterior aspect and covered by a thin calvaria. In the squirrel monkey, the cerebellum is overlapped by the occipital lobes thicker calvaria and thick muscles in the cervicle regions [Albert et al., 1981b]. Thus, too many variables are different for the two experiments to be truly comparable.

Guy and Chou [1982] histologically examined the brains of six rats exposed to 25–42 kJ/kg of 915 MHz single pulse (0.1 s) energy. The SARs ranged from

TABLE 3. Effects of RF Exposure on Nervous System Morphological Changes

Effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
Damage to cells' membrane is different from the damage caused by simple heating, cell membranes appear to be a specific target for RF injury	Mouse (neuroblastoma cells)		2700	PW	1.7–3.9 kV/cm	30–60 s	Webber et al. [1980]
Significant and irreversible decrease cerebellum Purkinje cells	S–D rats	2.77	100	CW	46	4 h/day × 97 days	Albert et al. [1981a]
		2.0	2450	CW	10	21 h/day × 5 days	
No change in cerebellum Purkinje cell numbers	Monkeys	3.4	2450	CW	10	3 h/day × 9 months	Albert et al. [1981b]
Endoplasmic reticulum slight swelling and Golgi complex dilation (subesophageal ganglia from *Helix aspersa* snails)	*Helix aspersa* snails	12.9	2450	CW		60 min	Arber et al. [1986]
Petit or grand mal seizure for 1 min after exposure. Histological exam showed some demyelination or neurons 1 day after exposure and some microfocal glial nodules I month postexposure	Rats	25.8 kJ/kg	915	PW with PD 1 μs to 360 ms	2–10 kW	0.1 s	Guy and Chou [1982]

250 to 417 kW/kg and the temperature rise was from 8 to 13.5 °C. There were some unilateral focal and microfocal encephalomalacia, which was due to demyelination of neurons in the dorsal frontal cerebral cortex 1 day after exposure. One month later, the only pathological findings in two exposed rats were: (1) that brains appeared swollen and (2) in one rat a few microfocal glial nodules were present in the basal ganglia anterior to the optic nerves, while in the other a single microfocal glial nodule appeared in the cerebral cortex.

Exposing subesophageal ganglia from *Helix aspersa* snails to 2.45 GHz MW (SAR 12.9 W/kg for 60 min), Arber et al. [1986] found that MW exposure at 21 °C caused minor changes in Golgi complexes and a slight swelling of the endoplasmic reticulum. In two experiments where the left parietal and visceral ganglia were used as control and the right parietal ganglion separated from the same ganglionic mass was exposed to MW at 8 °C, they failed to detect any morphological differences between the control and the irradiated neuronal cell bodies. In this work, with a constant bath temperature maintained throughout the exposure period, intracellular hot spots can be excluded.

This brief cell morphology literature review suggests that alteration of structure of cells within a living animal requires a thermalizing dose rate.

Blood–Brain Barrier (BBB) Permeability

The blood–brain barrier (BBB) prevents high molecular weight substances in the blood from getting into the brain. This barrier protects the brain from foreign toxic substances but allows passage of the molecules that are necessary for metabolism. A number of causes, such as edema, anoxia, hypertension, and ionizing radiation, have been shown to induce BBB changes, often increasing permeability of substances to the brain. The radio tracer method of Oldendorf [1970] is often used to allow for a quantitative measurement of test substance penetration. The RF induced BBB permeability increase was controversial for many years. Now most researchers believe that the permeability change is associated with an increase in temperature induced blood flow. BBB effects are summarized in Table 4.

Sutton et al. [1973] found that 2.45 GHz induced hyperthermia affects the BBB in rats. In contrast, Frey et al. [1975] reported that a 30 min, 1.2 GHz CW exposure at 2.4 mW/cm^2 (SAR ~1 W/kg) could induce a statistically significant increase in BBB permeability. They also reported that pulsed wave exposure was more effective than CW. Oscar and Hawkins [1977] exposed rats to 1.3 GHz energy and found that exposure to MW energy, either pulsed wave or continuous wave, induced increases in the uptake of D-mannitol at less than 3.0 mW/cm^2 average power density. The results also indicated that permeability changes occurred in the medulla, cerebellum, and hypothalamus, in decreasing order. It was observed that, after an initial rise, cerebral vessel permeability to saccharides decreased with increasing MW power. Different pulse characteristics caused different uptake levels. Albert and Kerns [1981] exposed Chinese hamsters to 2.45 GHz CW fields for 2 h at 10 mW/cm^2 and showed that the increased BBB permeability is reversible.

In many follow-up studies, most researchers could not replicate the BBB permeability changes [Merritt et al., 1978, 1982; Preston et al., 1979; Chang et al., 1982; Gruenau et al., 1982; Ward et al., 1982; Ward and Ali, 1985] or could show the effect only at high intensity levels, when the heating of the brain tissue was obvious [Lin and Lin, 1980, 1982; Goldman et al., 1984; Neilly and Lin, 1986; Moriyama et al., 1991; Ikeda et al., 1994; Ohmoto et al., 1996]. Williams et al. [1984a–d], in a series of four articles, reported their extensive studies using several tracers and methods for detecting rat BBB permeability alterations after 2.45 GHz MW exposure, but they could not find the effects unless the temperature was elevated above 40 °C. Oscar et al. [1981] measured the blood flow rate in rats exposed to 2.8 GHz pulsed fields at 15 mW/cm^2 for 5–60 min and found that the exposure increased the blood flow. They called for reevaluation of their previous findings in the BBB permeability change.

A few positive effects at low exposure intensities were reported. Neubauer et al. [1990] exposed male albino rats to pulsed, 2.45 GHz MW 10 μs and 100 pps, at a low average power density of 10 mW/cm^2 (2 W/kg) for short durations (30–120 min); the results showed increased uptake of tracers through the blood–brain barrier. Changes in BBB permeability are dependent on power density and on the exposure duration. Salford et al. [1993] showed that both continuous and pulse modulated, 915 MHz MW 0.57–4 ms pulses, modulated at 8, 16, 50, and 200 Hz can open up the BBB for albumin passage in Fisher 344 rats. No significant differences between continuous and pulsed 915 MHz MW were observed. They did not monitor the brain temperature in their study.

In a second article, Salford et al. [1994] showed more SAR information. However, the SAR data were estimated from the E field in the TEM cell. Since the E field in the TEM cell is not the same as that in the rat brain, the SAR estimate was incorrect. Prato et al. [1990] showed that after 23 min of magnetic resonance imaging (MRI), rats had significantly greater retention of [^{153}Gd]DTPA than sham exposed rats. These findings suggest that MRI increases BBB permeability. The RF used was 6.25 MHz, but the SAR in rat brain is

TABLE 4. Effects of RF Exposure on Blood–Brain Barrier (BBB)

Effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
Measured increased cerebral blood flow rates	Rats		2800	PW	15	5–60 min	Oscar et al. [1981]
Increase BBB permeability by Evans blue dye, which is related to intense MW hyperthermia	Rats	~3.0	2450	PW		20 min	Lin and Lin [1982]
No significant increase in permeation after correcting the δ for thermal effects of the MW exposure, using [^{14}C] and [^{3}H] as tracers molecules	CD albino rats	0, 2, 4, or 6	2450	CW	0, 10, 20, or 30	30 min	Ward et al. [1982]
No increase in permeation effects on the BBB were observed, 131 I albumin as a tracer molecule	Mongrel dogs		1000	CW	2, 4, 10, 50, or 200	20 min	Chang et al. [1982]
Attempts to alter $^{45}Ca^{2+}$ binding to brain tissue with pulse-modulated MW energy	Rat brain in vivo and in vitro	1.9–2.9	1000	PW	1	20 min	Merritt et al. [1982]
		0.3	2450		10		
Absence of MW effect on BBB permeability to [^{14}C] sucrose in the conscious rat			2800	CW and pulsed at 500 pps	10–40 CW; 1–15 PW	30 min	Gruenau et al. [1982]
Increase BBB permeability to sodium fluorescein was found only in the brain made considerably hyperthermic by exposure to ambient heat or RF energy	Fisher- 344 rats	13 (>41 °C)	2450	CW	65	30 or 90 min	Williams et al. [1984a]
No increase in BBB permeability to HRP following exposure to ambient heat or MW, actually, a reduced uptake of the tracer by the brain was observed	Fisher- 344 rats	13	2450	CW	0, 20, or 65	30, 90, 180 min	Williams et al. [1984b]
No increase in BBB permeability to tracer [^{14}C]	Rats	13	2450	CW	20 or 65	30 or 90 min	Williams et al. [1984c]
No change in uptake of either [^{14}C] or [^{3}H] tracer was found in any of the eight brain regions as compared with those of sham-exposed animals	CD rats	0.1	1700	CW and PW		30 min	Ward and Ali [1985]
Increase of BBB permeability to [^{86}Rb] are associated with intense, MW-induced hyperthermia, and that the observed changes are not due to field-specific interaction	Wistar-derived rats	Average 3, a peak: 240	2450	PW		5, 10, or 20 min	Goldman et al. [1984]
Ethanol inhibits MW-induced permeation of the BBB through reduced heating of the brain	Wistar rats	3.0	3150	CW		15 min	Neilly and Lin [1986]

Magnetic resonance imaging increases the BBB permeability to $_{153}$gadolinium diethylenetriaminepentaacetic acid in rats			6.25			23 min	Prato et al. [1990]
Increase uptakes of an intravascular molecule (Rh–F complex) through the BBB	Albino rats	~2	2450	PW	10	30–120 min	Neubauer et al. [1990]
Both continuous and pulsed MW are able to open up the BBB for albumin passage	Fisher-344 rats	3.3	915	CW and PW			Salford et al. [1993]
Extravasation was independent of SAR <2.5 W/kg but rose significantly for higher SAR and was not significantly different between pulse and CW exposure conditions	Fisher-344 rats	0.16–5	915	CW and PW; 8, 16, 50 200/s		120 min	Salford et al. [1994]
Nerve cell damage in mammalian brain after exposure to MW from GSM mobile phones	Rats, aged 12–26 weeks	WB-SARs 2, 20, and 200 mW/kg	862–960	PW: 217 Hz	Peak power densities: 0.24, 2.4, and 24 W/m^2	2 h	Salford et al. [2003]
Extravasation of Evans blue was observed in the regions where the temperature reached 43 °C and above, but not in the areas where the temperature was 42 °C and below	Wistar rats	<43 °C	8	CW		30 min	Ohmoto et al. [1996]
Opening the BBB is due to MW-induced hyperthermia, not related to the nonthermal effect of MW	S–D rats	42.5 or 44.3 °C	2450	CW		30 or 60 min	Moriyama et al. [1991]
Immunohistology against rat's own albumin: extravasation only at 7.5 W/kg	Rat	0.3–7.5 Brain	900 MHz	GSM		4 h	Fritze et al. [1997]
Immunohistology against rat's own albumin and fibrinogen. avidin–biotin: extravasation at all SAR levels	Rat	0.0012–12 Whole body	915 MHz CW and GSM:	217 Hz with 0.57 ms pulse width, or at 50 Hz with 6.6 ms pulse width		From 2 min to 960 min	Persson et al. [1997]
Immunohistology against rat's own albumin. avidin–biotin Evan's Blue: no extravasation	Rat	2 Brain	1439 MHz	GSM TDMA		1 h/day, 2–4 weeks	Tsurita et al. [2000]
In vivo immunohistology against mouse's own albumin No extravasation	Mice	4.0 Whole body	898.4 MHz	GSM		60 min	Finnie et al. [2001]
In vitro model of BBB immunohistology against ZO1 ^{14}C. sucrose flux: increased permeability	Mice	0.3	1800 MHz	GSM		4 Days	Schirmacher et al. [2000]
Effect of long-term mobile communication MW exposure on vascular permeability in mouse brain. No extravasation	Mice	0.25, 1.0, 2.0, and 4.0 W/kg whole body	898.4 MHz	GSM		60 min, 5 days/week for 104 week	Finnie et al. [2002]

unknown. The authors suggested that the effect might be due to the time varying magnetic field, and they considered the nonreplication of the effect of others was due to differences in MRI parameters. Without the temperature information, it is difficult to evaluate whether or not the effect is thermal. The SAR values could be underestimated when the field is pulsed.

Persson et al. [1997] evaluated the effects of CW and pulsed 915 MHz exposure on the BBB in the rat brain. Following CW exposures, the number of rats exhibiting increased BBB permeability was elevated, but this change did not vary with SAR in the range of 0.02–8.3 W/kg. The results with modulated exposure were not dependent on SAR either. This and previous studies [Persson et al., 1992; Salford et al., 1993, 1994, 2003], which reported that nonthermal levels of cell phone related RF exposure altered the BBB in the rat, have generated some controversy. However, these studies report that BBB leakage in the brain does not follow a dose response function or a consistent pattern of modulation effects.

Recent attempts to replicate these findings have so far been unsuccessful [Fritze et al., 1997; Tsurita et al., 2000; Finnie et al., 2001, 2002]. Tsurita et al. [2000] failed to show BBB, cerebellum Purkinji cell, or body weight changes in rats, following 1.44 GHz TDMA exposures at SARs up to 2 W/kg. Fritze et al. [1997] measured albumin leakage in rats exposed for several days to 900 MHz GSM MP exposure. They found leakage only at the highest SAR of 7.5 W/kg. Similar results were found when albumin leakage was measured in mice exposed to 898.3 MHz GSM MP exposure [Finnie et al., 2001, 2002]. Schirmacher et al. [2000] with an in vitro model using immunohistology against ZO1 ^{14}C sucrose flux, noticed increased permeability at 0.3 W/kg. Overall, the BBB leakage studies report both positive and negative findings. At high SAR levels, the effects are consistent with local temperature elevations in the brain and increased blood flow. At lower SARs, the BBB effects are inconsistent with the other findings.

Microwave and Drug Interaction

Michaelson et al. [1961] reported that the thermal response of dogs exposed to 2.8 GHz, 165 mW/cm^2, was aggravated under the influence of chlorpromazine, morphine sulfate, or pentobarbital sodium. Baranski and Edelwejn [1968] found EEG changes in rabbits injected with chlorpromazine, a cortical activity depressant, and exposed to 3 GHz PW at an estimated SAR of 3 W/kg. The effect was different with the drug alone. Pulsed microwaves, even at very low incident power densities, can induce auditory responses (see Elder and Chou [2003] in this issue). In addition, metal electrodes were used for EEG recording. Therefore, the interpretation of this EEG effect may be invalid. In the 1970s, Servantie et al. [1974], Goldstein and Sisko [1974], Wangemann and Cleary [1976], and Thomas et al. [1979] showed combination effects of drugs in mice, rats, and rabbits exposed to pulsed and CW microwaves. MW and drug interaction studies are summarized in Table 5.

Lai et al. [1983, 1984a,b, 1986a], in a series of experiments, used the same exposure method and parameters to study the effects of various psychoactive drugs in rats exposed for 45 min in circularly polarized, pulsed MW fields (2.45 GHz; 2 μs pulses, 500 pps). A review of the MW exposure and psychoactive drugs was published by Lai et al. [1987c]. They showed that apomorphine induced hypothermia and stereotypic behavior were enhanced by MW exposure. Amphetamine induced hyperthermia was attenuated while stereotypic behavior was unaffected. Lai et al. [1986a] found that the amphetamine-induced hyperthermia can be classically conditioned to cues in the exposure environment after repeated exposure and the effect can be blocked by antagonist drug naloxone. Morphine induced catalepsy, different modes of action on central neural mechanisms, and the effects of MW depend on the particular drug studied. MW prolonged the narcolepsy and hypothermia induced by pentobarbital [Lai et al., 1984e]. SAR in the head correlated with the MW effect on the pentobarbital induced hypothermia, while the whole body averaged SAR was the same. Ethanol induced hypothermia and ethanol consumption in rat are also affected by MW exposures [Lai et al., 1984b]. This last finding was later replicated by Hjeresen et al. [1988]. Neilly and Lin [1986] exposed one side of the rat heads to show that the ethanol inhibits MW induced permeation of the blood–brain barrier through reduced brain heating.

Lai et al. [1986b] showed that MW exposure attenuates the naloxone induced withdrawal syndrome in morphine dependent rats. The MW exposed rats showed significantly less wet-dog-shakes and had a higher body temperature than the sham exposed animals during withdrawal. Frey and Wesler [1990] reported that exposure of rats to 1.2 GHz pulsed microwaves 11 pps, 20 μs, 8 μW/cm^2 averaged power density, affected the action of naloxone, chlordiazepoxide, and haloperidol on analgesia and stereotypic behavior. The authors believe that the effect is due to the MW energy affecting the dopamine-opiate systems of the rat brain. The average power density appears very low, since the pulse repetition rate was only 11 pps.

At thermal levels, Jauchem et al. [1984] reported no effect of atropine sulfate and propranolol on body temperature of ketamine anesthetized rats exposed to

TABLE 5. Interaction Effects of RF Exposure and Drugs

Effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
Enhance anticholinesterase drug (phospholine iodide) hypothermia effect	Tac:N (SD) fBR rats		2800	PW	10	10 min	Ashani et al. [1980]
Enhance apomorphine-induced hypothermia and stereotype, attenuated amphetamine-induced hyperthermia while unaffected stereotype	S–D rats	0.6	2450	PW	1.0	45 min	Lai et al. [1983]
Ethanol inhibits MW-induced permeation of the BBB through reduced heating of the brain	Wistar rats	3.0	3150	CW		15 min	Neilly and Lin [1986]
No effects on drug (pentobarbital) absorption and distribution and pentobarbital-induced fall in colonic temperature (irradiated followed by drug injection; the core temperature in pentobarbital anesthetized but not in conscious rats drug injection followed by irradiation)	S–D rats	0.6	2450	PW	1.0	45 min	Lai et al. [1984a]
Enhance ethanol-induced hypothermia, the nature of possible RF effects remains to be fully elucidated	Rats	0.3	2450	CW	1.5 or 3.0	45 min	Hjeresen et al. [1989]
Administration of amitriptyline, haloperidol, or saline did not significantly affect thermal responses, while chlorpromazine can counteract hyperthermia during exposure to radiofrequency radiation	S–D rats	14	2800	CW	60		Jauchem et al. [1984]
Attenuate naloxone-induced withdrawal syndrome in morphine-dependent rats, it was due to RF activates endogenous opioids in the rats	S–D rats	0.6	2450	PW	1.0	15 min	Lai et al. [1986a]
A single acute exposure to a thermogenic level of MW irradiation facilitates methylatropine antagonism of centrally medicated cholinomimetic drug effects	ICR mice	23.7	2450	CW		10 min	Quock et al. [1986]
Increase choline uptake activity in the frontal cortex, hippocampus, and hypothalamus, this effect could be blocked by pretreating the animals before exposure with the narcotic antagonist naltrexone; decrease in concentration of receptors occurred in the frontal cortex and hippocampus	S–D rats	0.6	2450	PW	1.0	20 or 45 min	Lai et al. [1989a]
Decrease sodium-dependent high-affinity choline uptake activity in the frontal cortex and hippocampus, these effects were blocked by injection of the specific corticotropin-releasing factor (CRF) receptor antagonist, a-helical–CRF9-41	S–D rats	0.6	2450	PW	1.0	45 min	Lai et al. [1990]
Induce biphasic changes in the concentration of muscarinic cholinergic receptors in the central nervous system: increase in the hippocampus exposed to ten 45-min sessions, but decrease in the frontal cortex to ten 20-min session	S–D rats	0.6	2450	PW	1.0	20 or 45 min	Lai et al. [1991]
Decrease cholinergic activity in the hippocampus, all three subtypes of opioid receptors are involved in this effect, but this effect in frontal cortex was not affected by any of the drug treatments	S–D rats	0.6	2450	PW	1.0	45 min	Lai et al. [1992]
Inhibit the scopolamine induced reduction in latencies associated with shock conditioning during subsequent testing; decrease locomotor activity, it appears to be enhanced by the simultaneous administration of physostigmine	Mice	1 or 10	2450	CW		30 min	Monahan [1988]
Affect the chlordiazepoxide, naloxone, and haloperidol induced behavioral effects through dopamine-opiate system	Rats		1200	PW	0.8		Frey and Wesler [1990]

2.8 GHz, 14 W/kg PW. Later in 1985, they investigated the effects of chlorpromazine, amitriptyline, and haloperidol on thermal responses in anesthetized rats exposed to 2.8 GHz RF energy (SAR 14 W/kg) [Jauchem et al., 1985]. Administration of amitriptyline (10 mg/kg), haloperidol (0.1 mg/kg), or saline did not significantly affect thermal responses. Acute administration of chlorpromazine could counteract hyperthermia during RF exposure when colonic temperature was kept below 39.5 °C. Quock et al. [1986] reported that pretreatment with methylatropine (1.0 mg/kg) or exposure to 2.45 GHz, 23.7 W/kg CW for 10 min, did not appreciably affect the dose–response curves for pilocarpine induced hypothermia and oxotremorine induced tremors in mice. However, in mice receiving both the methylatropine pretreatment and MW exposure, the dose–response curves for both effects were significantly shifted to the right, signifying a central anticholinergic action by methylatropine. These data indicate that a single acute exposure to a thermogenic level of MW energy facilitates methylatropine antagonism of centrally medicated cholinomimetic drug effects.

At this SAR level, it is possible that the MW exposure enhanced the passage of quaternary ammonium compounds across the BBB and blood–cerebral spinal fluid barrier. However, at low power densities, it is questionable that the BBB permeability is changed during exposure. The change in local blood flow due to different SAR distributions might alter the drug distribution in the brain [Lai et al., 1987c]. The auditory system is very sensitive to pulsed MW exposure [Chou et al., 1982]. Lai [1992] found many effects were elicited by PW but not CW exposures. This sensory input can affect the brain functions and alter the actions of psychoactive drugs. More possible mechanisms of the effect can be explored by studies on the neurochemistry.

Neurochemistry

Psychoactive drugs affect neural functions by modifying neurotransmitter activities. If MW can affect transmitter actions, the drug effects described in the previous section can be explained. Studies on neurochemistry and especially on neurotransmitters may reveal the mechanisms of drug and MW interaction. Studies for this section are summarized in Table 6.

In the 1970s, Snyder [1971] studied 3 GHz CW exposure effects on the 5-hydroxyindolacetic acid and serotonin in rats. Opposite effects were found depending on exposure level. Zeman et al. [1973] found no effect on GABA levels and L-glutamate decarboxylase between control and 2.86 GHz pulsed exposure for either acute (8 W/kg for 20 min) or chronic exposure (2 W/kg for 4 or 8 h daily and up to 4 or 8 weeks). Merritt et al. [1976, 1977] exposed rats at thermal levels (80 mW/cm^2) and observed effects on norepinephrine, dopamine, and serotonin.

Ashani et al. [1980] administered an anticholinesterase drug (phosphine iodide) to rats and 10 min later exposed them to pulsed 2.8 GHz MW energy at 10 mW/cm^2 for 10 min. This procedure produced a statistically significant decrease in body temperature when compared to various control groups. The enhancement of hypothermia in the presence of low level MW exposure was also observed when rats were injected with another inhibitor of acetylcholinesterase, paraoxon, and with 2-pyridine aldoxime methyl methaneulfonate, an antidote against anticholinesterase poisoning. Millar et al. [1984] found no significant effect of 2.45 GHz MW exposure on acetylcholinesterase (AChE) activity using a wide variety of power densities, pulse widths, repetition rates, and duty cycles. On the other hand, at very low SAR (0.01–0.05 W/kg), Dutta et al. [1992] reported increased and decreased AChE activity in neuroblastoma cells (NG108) exposed for 30 min to 147 MHz fields, amplitude modulated at 16 Hz. Enhanced activity was observed within a time window of 7.0 and 7.5 h after the cells were plated. They related RF effects in nervous system-derived cells in culture to both calcium ion release and AChE activity in a common dose dependent manner.

Lu et al. [1980] evaluated the effects of RF exposure on neuroendocrine responses. Rats were acclimated to experimental conditions and then subjected to 2450 MHz CW RF exposure at 1–70 mW/cm^2 or sham exposure for 1 h. Colonic temperature showed an increase with RF exposure greater than 20 mW/cm^2. The authors found that corticosterone, thyrotropin, and growth hormone levels were correlated with power density and colonic temperature in rats exposed to RF for 1 h.

Sanders et al. [1980] studied 591 MHz MW effects on the energy metabolism of rat brain, which included effects on nicotinamide adenine dinucleotide reduced (NADH), ATP and creatine phosphate (CP) levels. While there was no measurable brain temperature increase, there were changes in the parameters studied. In 1984, Sanders et al. found differential effects of 200 MHz, 591 MHz, and 2.45 GHz exposure on rat brain energy metabolism. Sanders et al. [1985] investigated the effects of continuous wave, pulsed, and sinusoidolly amplitude modulated MW (591 MHz) on brain energy metabolism. The MW induced increase in brain NADH fluorescence and decrease in ATP and CP concentrations were not due to brain hyperthermia. They suggested that a direct interaction mechanism is consistent with their hypothesis of MW inhibition of

TABLE 6. Effects of RF Exposure on Neurochemistry

Effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
Inhibit pituitary-thyroid function, increase serum corticosterone, decrease serum thyrotropin, and decrease serum growth hormone levels were correlated with power density or colonic temperature, body temperature influences adenohypophysial hormones	Long-Evans rats		2450	CW	1 or 70	1, 2, or 8 h	Lu et al. [1980]
Inhibit mitochondrial electron transport chain function, which results in decreased adenosine triphosphate and creatine phosphate levels the rats brain	S–D rats		591	CW	5.0 or 13.8	1, 2, 3, or 5 min	Sanders et al. [1980]
The NADH increased at 200 and 591 MHz, no effect at 2450 MHz. The ATP levels were decreased at 200 and 591 MHz but not at 2450 MHz. The CP levels decreased only at 591 MHz	S–D rats	0.02, 0.04,...or 40	200, 591, or 2450	CW	0.5,... or 40	1, 2, 3, or 5 min	Sanders et al. [1984]
Inhibit mitochondrial electron transport chain function of ATP production	S–D rats		591	CW, PW, or AM	13.8	5 min	Sanders et al. [1985]
Low frequency MW radiation alter the metabolism of inositol phospholipid by enhancing their turnover and thus may affect the transmembrane signaling in the nerve endings	S–D rats		2800	PW	10 or 30	30 min	Gandhi and Ross [1989]
Lower the amount of mitochondrial marker enzymes succinate dehydrogenase (SDH) and monoamine oxidase (MAO) in the hypothalamus and hippocampus in the irradiated groups (except 0.1 mW/cm), PW radiation is more effective then CW radiation in decreasing SDH and MAO levels	C57BL mice		2450 or 3000	CW or PW	0.1, 0.5, 1.0, or 5	3 h	Chiang et al. [1984]
Reduce SDH in the hypothalamus by either pre- or post-natal MW exposure, the same pattern appeared with hypothalamic catecholamine and MAO	Kuming mice		3000	PW	8.0	5 h/day × 18 days	Chiang and Yao [1987]
No significant effect on acetylcholinesterase enzyme activity; simple, direct modification by MW energy of acetylcholinesterase structure and enzymatic activity is not related to MW alteration of acetylcholinesterase central nervous system levels	*Narcine brasiliensis* fish	2.46 or 4.29	2450	PW			Millar et al. [1984]
Decreased cholinergic activity, the effect is site selective and dependent on the form of MW studied, but the mechanism by which MW affect central cholinergic functions is not clear	S–D rats	0.6	2450	CW or PW	1.0	45 min	Lai et al. [1987]
The effects of microwaves on choline uptake in the hippocampus and frontal cortex are classically conditionable, probably to cues in the exposure environment	S–D rats	0.6	2450	PW	1.0	45 min/day × 10–10 days	Lai et al. [1987]
Dose-response study. Decrease choline uptake in the striatum at a SAR of 0.75 W/kg and above, for the frontal cortex and hippocampus at a SAR of 0.45 W/kg and above. SAR50 values for the striatum, frontal cortex, and hippocampus were 0.65, 0.38, and 0.44 W/kg, respectively	S–D rats	0.3, 0.45, 0.6, 0.75, 0.9, or 1.2	2450	PW		45 min	Lai et al. [1989]
All three subtypes of opioid receptors are involved in the MW-induced decrease in cholinergic activity in the hippocampus. The MW-induced decrease in cholinergic activity in the frontal cortex was not affected by any of the drug treatments	S–D rats	0.6	2450	PW	1.0	45 min	Lai et al. [1992]
Enhance acetylcholinesterase (AchE) activity was observed within a time window between 7.0 and 7.5 h after the cells were plated and only when the exposure occurred at power densities identified in a previous report as being effective for altering the release of calcium ions	NG108–15 cells	0.001, 0.005, 0.01, 0.02, 0.05, or 0.1	147	PW		30 min	Dutta et al. [1992]
Decrease hypothalamus adrenergic receptors and increase muscarinic cholinergic receptors	S–D rats	20	700	CW	15	Temperature increase 2.5 °C	Gandhi and Ross [1987]
No neurotoxic, neither acute nor chronic MW radiation had any effect on the levels of synapsin I in the brains of irradiated rats	Rats	1 or 2	500, 2450, or 2800	CW or PW	1, 5, 10, 15, 20, or 50	30 min or 23 h × 7 days	Browning and Haycock [1988]

mitochondrial electron transport chain function of ATP production. Chiang et al. [1984] reported that 3 GHz MW can affect mitochondrial marker enzymes in mouse brain. Chiang and Yao [1987] showed that low intensity pulsed MW exposure could induce subtle succinate dehydrogenase alterations in developing mouse brain. Browning and Haycock [1988] examined the calcium dependent phosphorylation of synapsin I in synaptosomes isolated from rats that had been subjected to MW exposure. The results show that at nonhyperthermia levels, neither acute nor chronic MW exposure had any effect on the levels of synapsin I in the brains of irradiated rats.

Gandhi and Ross [1987] exposed rats to 700 MHz at 15 mW/cm^2, which raised the core temperature by 2.5 °C. They found that both norepinephrine and acetylcholine are released in response to heat. In 1989, the same authors studied MW exposure on rat brain synaptosomes and found that it alters the metabolism of inositol phospholipids by enhancing their turnover and thus may affect transmembrane signaling in nerve endings. Inaba et al. [1992] exposed rats to 2.45 GHz MW at thermal levels and found reduced norepinephrine, increased 5-hydroxyindoleacetic acid and no change in serotonin.

Lai [1992] has summarized his 10 years of research on the neurological effects of MW exposure. While studying the effects of various psychoactive drugs under MW exposure, he found that narcotic antagonists block the actions of endogenous opioids, which are involved in various physiological functions, such as stress response, thermoregulation, and analgesia. The hypothesis that MW exposure activated endogenous opioid systems is consistent with many of findings by Lai et al. [1984c,d, 1987c]. Effects on cholinergic systems were investigated since they are involved in many physiological and behavioral functions [Lai et al., 1988]. They first found that MW exposure reduced sodium dependent, high affinity choline uptake, an index of cholinergic activity, in the frontal cortex and hippocampus of rat. The observation that the effect on the hippocampus can be blocked by a narcotic antagonist, but not the effect on frontal cortex, is similar to a response to acute restraint induced stress [Lai et al., 1987a,b]. The effect also could be conditioned to cues in the environment. A learning deficit was found to be correlated to the decrease in cholinergic activity [Lai et al., 1989a]. When the exposure time was reduced from 45 to 20 min, the cholinergic activity was increased instead of decreased [Lai et al., 1989b]. Changes in muscarinic cholinergic receptors were investigated. The receptor effect was found to be opposite from the cholinergic activity effect for 20 and 45 min exposures [Lai et al., 1989b]. The receptor effect also depended on endogenous opioids in the brain because it was blocked by the narcotic antagonist naltrexone [Lai et al., 1991]. Probing further into which subtype of opioids receptor was affected, Lai et al. [1992a] found all three subtypes were involved.

Based on the above results, Lai et al. [1992a] proposed a model of neural mechanisms mediating the effects of low level MW on cholinergic activity in the frontal cortex and hippocampus of the rat. The 45 min MW exposure somehow activated the corticotropin-releasing factor, which in turn caused a decrease in activity of cholinergic innervations in the frontal cortex and hippocampus [Lai et al., 1990]. The endogenous opioids, via three receptors, are the intermediate step before the hippocampal change occurs. The activation process might be a stress response. Lai et al. [1992b] tested this possibility by studying the concentration of benzodiazepine receptors in the cortex and hippocampus. The increased level in the cortex showed adaptation after repeated exposure, i.e., less stress. These data might explain the results of Thomas et al. [1979] and Hjeresen et al. [1989]. Monahan [1988] reported that 2.45 GHz CW (SAR 1 and 10 W/kg) affects the cholinergic drug scopolamine and physostigmine on shock latency and motor activity of mice. These data also suggested MW enhancement of cholinergic activity.

Animal studies have shown that RF exposure can alter the neuroendocrine system [Michaelson et al., 1975; Lu et al., 1980]. De Seze et al. [1999] looked for changes in hormone levels, such as the amount of melatonin secreted from the pineal gland in humans. They did not find melatonin changes related to MP relevant exposures. These investigators also studied anterior pituitary hormones (serum adrenocorticotropin, thyrotropin, growth hormone, prolactin, luteinizing hormone, and follicle stimulating hormone) and did not find significant alterations following exposures [de Seze et al., 1998]. Mann et al. [1998] exposed humans to low level 900 MHz MW at night and found no changes in serum melatonin levels. Vollrath et al. [1997] also failed to find nocturnal melatonin changes in rats exposed to 900 MHz at SARs 0.1–0.6 W/kg. Radon et al. [2001] demonstrated a lack of effect of 900 MHz fields on salivary assays for melatonin, cortisol, neopterin (cellular immune activity), and immune globulin A. Eight human males, exposed or sham exposed to pulsed fields (217 Hz, 1 W/m^2) for 4 h periods (across night and day) in a double blind study, did not find significant effects. Mausset et al. [2001] evaluated the effects of pulsed 900 MHz fields on the γ-aminobutyric acid (GABA) neurotransmitter system in the cerebellum of rats. Rats were exposed to pulsed fields at an SAR of 4 W/kg or to CW fields at 32 W/kg for 2 h periods. Both

exposures resulted in diminution of GABA content in the cerebellum. Since only one dose rate was used for each type of exposure (CW or PW), one can only assume that local heating, once again, is responsible for the effects.

PERIPHERAL NERVOUS SYSTEM AND ISOLATED TISSUE

In the 1960s and 1970s, in vitro studies on isolated nervous tissues were conducted in the United States and Soviet Union. Various waveguides and exposure chambers were used to expose nerves, ganglia, and nerve–muscle preparations. Thermal effects were difficult to separate from the specific MW effects, if there were any. Courtney et al. [1975] and Chou and Guy [1978] used a temperature controlled waveguide to expose frog sciatic nerves, cat saphenous nerves, rabbit vagus nerves, and rabbit superior cervical ganglia as well as rat diaphragm muscles to 2.45 GHz CW or PW. No specific MW effects were observed. Observed effects could be reproduced by changing the solution temperature. It was shown that a temperature rise in the solution as small as 0.2 °C could induce observable effects on action potential latency or muscle contraction [Chou and Guy, 1978].

The studies discussed in this section are listed in Table 7. McRee and Wachtel [1980, 1982] studied the effects of CW and pulsed 2.45 GHz MW exposure on the vitality of isolated frog sciatic nerves in a temperature controlled waveguide exposure. In the CW study, a SAR of 10 W/kg significantly shortened the survival time of the irradiated nerve when stimulated to fire at a high rate (50 twin pulses per second). Below 5 W/kg, there was no effect. In the PW study, results showed that the increased rate of loss of exposed nerve vitality did not depend upon MW pulse synchronization with the firing of the nerve action potential. No significant differences were found in the loss of vitality of the CW and PW using the analysis of variance. The data indicated that MW effects on vitality depend on average SAR rather than peak SAR. When the Na–K pump was blocked by treatment with ouabain, the MW effect on the vitality of nerves was eliminated [McRee and Wachtel, 1986]. This result suggests that the nerve vitality effect is associated with the failure to maintain ionic gradients by active transport.

Pakhomov et al. [1991] used CW and PW 6.45 GHz MW, synchronized with stimuli or asynchronous and lasting for 10–50 min at SAR 30–230 W/kg, on the giant axon of the isolated earthworm ventral nerve cord. They found only a thermal effect. Different characteristics of giant nerve fiber function, including action potential (AP) velocity, refractory processes and vitality, were not perturbed by the field. Under some experimental conditions, the nerve appeared to have extreme sensitivity to subtle temperature changes induced by exposure, but no nonthermal MW effects were detected. At 40–52 GHz, Pakhomov et al. [1997] found no effect on the compound action potentials of isolated frog sciatic nerves when they were stimulated with low rate electrical stimulation; at high SAR levels the effects were reproducible with conventional heating. The fact that the effect at high rate electrical stimulation cannot be explained by thermal effect needs further investigation. Khramov et al. [1991] showed that the 34–78 GHz MW effect on the spontaneous firing rate of crayfish stretch receptor neurons is thermal. Effects of 75 GHz millimeter waves on the firing rate of BP-4 pacemaker neuron of the pond snail Lymnaea stagnalis were studied by Alekseev et al. [1997]. Exposure at an SAR of 4200 W/kg caused a biphasic change in firing rate, which is reproducible by simulating both the rate and final temperature rise. Addition of ouabain, a sodium pump inhibitor, eliminated the effect.

The findings of Tattersall et al. [2001], described above, on evoked and spontaneous potentials in rat hippocampal slices are interesting. The authors suggest that such excitability changes may be consistent with reported behavioral changes in vivo since the hippocampus is associated with memory and spatial learning, but this is, by their admission, quite speculative. Pakhomov et al. [2003] did not observe changes on evoked and spontaneous potentials using a similar hippocampal slice neuronal preparation following 9.3 GHz (AM: 0.5–10 Hz) exposure. The peak SAR in the brain slices reached 500 MW/kg and MW heating of the tissue ranged from 0.5 °C (0.3 kW/kg average SAR) to 6 °C (3.6 kW/kg). The primary effect observed was a transient decrease in the PS amplitude, which was fully reversible. The authors state that this response was characteristic of a temperature response and not due to any other specific parameter of the PW. In comparing their work with that of Tattersall et al. [2001], the authors point out that of the over 400 brain slices studied to date, no positive effect could be found without a temperature increase of the preparation of at least 0.5 °C, whereas Tattersall et al. [2001] elicited variable effects, comparatively, with no measurable increase in preparation temperature. Pakhomov et al. [2003] point out that "if the reported nonthermal effects are unambiguously replicated under artifact-free conditions, this finding could have a major impact on modern MW biology and RF exposure safety guidelines."

Bolshakov and Alekseev [1992] exposed *Lymnaea stagnalis* neurons to CW and PW 900 MHz waves. The probability of burst-like irregularity was enhanced

TABLE 7. Effects of RF Exposure on Peripheral and Isolated Nerve Tissues

Effect	Species	SAR (W/kg)	Frequency (MHz)	Modulation	Intensity (mW/cm^2)	Duration	Reference
Increase the vitality of the exposed nerves loss rate, it depend on the average SAR rather than the peak SAR, no significant differences were found in the loss of vitality of the CW and PW	Isolated frog sciatic nerves	0.0010 W/kg	2450	CW or PW			McRee and Wachtel [1982]
No significant difference in the survival time of ouabain-treated exposed and control nerves, the relative loss of excitability in MW-exposed nerves is related to an interference with or counteraction of the Na–K pump	Isolated frog sciatic nerves	10	2450	CW			McRee and Wachtel [1986]
No effects on giant nerve fiber function, including action potential, velocity, refractory processes, and vitality	Earthworm	30–230	6450	CW or PW		10–50 min	Pakhomov et al. [1991]
Biphasic response during exposure. Decreased firing rate in BP-4 pacemaker neuron followed by gradual increaseof firing rate in pond snail. Effect was temperature and temperature rate increase dependent	Pond snail *Lymnaea stagnalis*	600–4200	75 GHz	CW		2–22 min	Alekseev et al. [1997]
Recorded extracellular field potentials in statum pyramidal or stratum radiatum of CA1 or CA3 hippocampal regions. Potentiation of amplitude of population spike by 20% at low field intensities	Rat		700	CW	25.2–71.0 V/m	5–15 min exposures	Tattersall et al. [2001]
Millimeter wave effects on compound action potential (CAP) were studied in isolated sciatic nerve. Exposure at low power did not alter CAP or refractory. At higher power subtle decrease in CAP latency that was mimicked by conventional heating	Isolated frog sciatic nerves		40–52 GHz	CW	0.24–1.5 and 2–3	10–60 min	Pakhomov et al. [1997]
Evaluated extremely high peak power pulses on (EHPP) on isolated hippocampal model using Schaffer collateral stimulation of CA1. Recorded population spikes which decreased during exposure but were fully reversible with no long term effects	Rat	500 MW/kg	9.3 GHz	PW 0.5–2 μs PD and 0.5–10 Hz			Pakhomov et al. [2003]
Exposure of neurons to CW inhibited spontaneous activity while AM exposure caused excitatory responses. The effect differed qualitatively from the inhibition after CW exposure	Snail *Helix aspersa*	12.9 and 6.8–14.4	2450	CW and amplitude modulated		60 min	Arber and Lin [1985b]

by PW exposure above 0.5 W/kg, but not CW. Arber and Lin [1985a] and Ginsburg et al. [1992] studied 2.45 GHz MW (SAR: 12.5–125 W/kg) on the input resistance, membrane conductance, and action potential in snail neurons. The changes were not consistent and the authors suggested that MW exposure may enhance degenerative effects in neuron metabolism. Arber and Lin [1985b] also reported modulation and temperature effects on the MW induced changes in snail neurons.

HEADACHE AND MICROWAVE EXPOSURE

Frey [1998], in a commentary, concluded that headaches could be caused by the use of MPs. He cited three lines of evidence that he felt led to his conclusion. First, earlier studies investigating the MW hearing effect used frequencies, modulations, and incident power densities to cause headaches that are very similar to those in use now with current MPs. Second, low level MW exposure alters the permeability of the BBB. And third, dopamine-opiate systems in the brain are thought to be involved in headaches.

More recently, several studies have examined symptoms reported during or after MP usage. Hocking [1998] conducted a survey to characterize the symptoms reported by MP users. Forty respondents to a request in a major medical journal were interviewed by telephone using a questionnaire. They described a burning feeling or a dull ache primarily in the side or back of the head or around the ear. Interestingly, the respondents, as summarized by Hocking [1998], said that the ''symptoms often began minutes after beginning a call, but could come on later during the day. The symptoms usually ceased within an hour after the call, but could last until evening.'' As the author points out, further work is needed to determine the range of effects, their mechanism, and the possible implications for safety limits of RF exposure. Sandstrom et al. [2001] evaluated symptoms of 2500 respondents to a survey to test the hypothesis that digital MPs produce more symptoms than analogue phones. The results of the survey disproved this hypothesis, although the data showed associations between calling time, number of calls per day, and the prevalence of warmth behind or on the ear. Oftedal et al. [2000] conducted a cross-sectional epidemiological study of 17 000 Norwegian and Swedish people who use a MP in their job. Of those responding, 31% in Norway and 13% in Sweden reported that they had experienced at least one symptom in connection with using their MPs. The most commonly reported symptoms included sensations of warmth on the ear and behind and around the ear, burning sensations in the facial skin, and headaches. The symptoms usually began during or within half an hour after the call and could last for up to 2 h. The authors reported that about 45% of those responding said they had taken steps to reduce the symptoms. Very few had consulted a physician or taken sick leave. The authors pointed out that the results suggested ''an awareness of the symptoms, but not necessarily a serious health problem.'' Chia et al. [2000a,b] also conducted a cross-sectional epidemiological study in Singapore to evaluate symptoms relevant to MP use. They studied a total of 808 men and women between 12 and 70 years of age of which 44.8% were MP users with responses to a structured questionnaire. Headache was the most reported symptom, which increased with duration of usage. Other symptoms were not reliably associated with MP usage.

While the association between nervous system symptoms and MP exposure in each of these studies is seemingly significant, many factors could influence the outcome; and all studies lack strength in providing a cause and effect relationship.

HUMAN ELECTROMAGNETIC HYPERSENSITIVITY

Electromagnetic hypersensitivity (EHS) is a term used to describe people who believe they are influenced by electric and magnetic fields from a variety of sources, including power lines, mobile telephones, household appliances, visual display monitors, and light sources [COMAR, 2002]. Generally, the fields that elicit EHS are reported to be very weak, well below what is known to affect normal individuals, and far below currently accepted safety standards. Individuals with EHS generally report a prevalence of symptoms that are related to the nervous system such as fatigue, stress, and sleep disturbances. The second most prevalent are skin symptoms, which include facial pricking, burning sensations, and rashes. These are followed in importance by various body symptoms (body ache and pain), eye symptoms (burning sensations), and less common ear, nose, throat, and digestive symptoms [Bergqvist and Vogel, 1997; COMAR, 2002]. The occurrence of EHS and associated symptoms varies geographically with a higher prevalence in Sweden, Germany, and Denmark.

Some studies have been done to evaluate EHS under controlled laboratory conditions. Hietanen et al. [2002] evaluated 20 people, self-reported as EHS to exposure from MPs, for sensitivity to 900 MHz analogue and 900 and 1800 MHz digital cell phone exposures. Subjects were evaluated for three or four 30 min sessions and asked to report any subjective feelings. During the test period, the heart rate, blood pressure, and breathing rate were recorded. The results

showed that subjects reported subjective symptoms, mostly in the head region; however, these were higher during the sham exposure than during real RF exposures. In addition, none of the test subjects could distinguish a real RF exposure from sham exposures. While subjective symptoms occurred, these could not be produced by the cell phones. A study by Flodin et al. [2000] compared 15 EHS subjects and controls. The EHS individuals were no better in detecting the electric and magnetic fields than were the controls.

These studies all suggest that the ESH individual is not better at detecting EMF and that EHS symptoms are not related to electric or magnetic field exposures. A COMAR [2002] report summarized many of the details of EHS. While EHS subjects fared no better at detecting EMF the report states that whatever its cause EHS is a real phenomenon which is a disabling problem for the affected individual.

One explanation, which seems quite plausible, was suggested by Anttila [2000], who proposed that ESH may be related to mycotoxins in the environment. Mycotoxins have shown, in animal studies, the same symptoms and effects as in EHS. Phototoxic reactions are well known in veterinary medicine and in medical science. The author points out that many of those displaying symptoms caused by EHS have fungus infections or have been living in fungus contaminated environments for long periods of time. The author offers the hypothesis that EHS is caused by 'phototoxic' reactions from fungal sources.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Developing health based exposure limits requires a detailed and lengthy review and evaluation of the scientific literature. This process begins with identification of a novel finding in a scientific study which was published in the scientific literature. Publication of the finding does not scientifically validate the study. There may be undiscovered errors in the conduct of the study or statistical significance may have occurred by chance. Instead, interest by other scientists motivates attempts of replication and generates additional hypotheses. Thus, validation of the original finding may follow from replication and complimentary studies. The finding then may be judged whether it is adverse or not. The SC4 IEEE C95.1 revision working group has defined adverse as:

> ''An adverse effect is a biological effect characterized by a harmful change in health. For example, such changes can include organic disease, impaired mental function, behavioral dysfunction, reduced longevity, and defective or deficient reproduction. Adverse effects do not include: biological effects without a detrimental health effect, changes in subjective feelings of well-being that are a result of anxiety about RF effects or impacts of RF infrastructure that are not related to RF emissions, or indirect effects caused by electromagnetic interference with electronic devices. An adverse effects exposure level is the condition or set of conditions under which an electric, magnetic, or electromagnetic field has an adverse effect.''

In setting safe limits for RF exposure it is often necessary to make assumptions about underlying mechanisms. A variety of mechanisms have been proposed to explain effects of RF exposure. As pointed out by Reilly [2000], with a mechanism model appropriate dosimetric measures and parametric relationships such as frequency and temporal factors can be evaluated. Reilly [1998; 2000] has reviewed interaction mechanisms and differentiates between established and proposed mechanisms. An established mechanism is defined as one where effects on a living person and thresholds of reaction are understood. On the other hand, a proposed mechanism is not sufficiently well understood and the threshold of interaction in a living person is not known or experimental results have not been established with confidence. Above a frequency of 100 kHz, there is ample evidence that much of what is known about the effects of RF exposure on the nervous system is based on thermal changes in surrounding tissues. Whether the changes in surrounding tissues are simply ''effects'' or are truly hazardous to an individual was aptly described by Michaelson and Lin [1987]:

> ''If an effect is of such an intense nature that it compromises the individual's ability to function properly or overcomes the recovery capability of the individual, then the 'effect' may be considered a 'hazard.' In any discussion of the potential for biological 'effects' from exposure to electromagnetic energies we must first determine whether any 'effect' can be shown; and then determine whether such an observed 'effect' is 'hazardous.' ''

Based on the review of the literature presented here it is difficult to draw conclusions concerning hazards to human health. There are several reasons for this difficulty. First, a large number of exposure parameters, such as frequency, orientation, modulation, power density, and duration of exposure, make direct comparison of the many experiments difficult. Also, the varied endpoint measures used in the different experi-

ments preclude direct comparisons. Clearly, at high enough exposure power densities, thermal effects are prevalent and can lead to adverse consequences. At lower levels of exposure, biological effects may still occur but thermal mechanisms are not ruled out. Evidence for specific effects that claim direct neuronal interactions with the RF fields is weak. In addition, most of the studies that claim provocative results have not been replicated by investigators or by independent laboratories.

Studies of EEG in experimental animals exposed to MW have been generally inconclusive. The early studies from the USSR and studies from the United States could not be compared because of the many differences in techniques and procedures. The joint collaborative studies designed to minimize the differences found some changes in spectral power of the EEG, but these were qualitatively different between the two laboratories. Other studies of human subjects exposed to MP emissions demonstrated effects on sleep, EEG, and evoked potentials during mental tasks. All of the positive results in studies of MW EEG interaction can be regarded as having little effect on the overall health and well being of the human subjects. Some studies that have reported low level effects can be discounted, due to the use of metallic electrodes, which cause artifacts. Within laboratories, effects on EEG have not been replicated. Between laboratories there is disagreement about RF effects on the EEG. As a result, no conclusions can be drawn from the present RF-EEG research.

Studies of morphological effects on animals have been conducted both in the Eastern European countries and the West. Eastern European studies reported that pulsed MW exposure has more marked effects than CW and that chronic exposure is more damaging than acute exposure. At high exposure levels, severe vascular disorders, such as edema and hemorrhages in the brain, were prominent. Western studies have examined brains of hamsters, rats, and monkeys after fetal and early life MW exposure. Rat cells showed effects, but the squirrel monkey cells did not. Certainly at high power exposures thermal effects are prominent due to demyelination of neurons. If heating and local hot spots are controlled, then effects at lower power levels do not occur. There are too few studies to draw conclusions about the health effects of the low level findings.

The BBB prevents high molecular weight substances in the blood from getting into the brain. This barrier protects the brain from foreign toxic substances, but allows the molecules that are necessary for metabolism to enter. Controversy has followed reports that MW caused leakage through the BBB. In many follow-up studies, most researchers could not replicate the low level BBB permeability changes or could show the effect only at high intensity levels, when the heating of the brain tissue was obvious. Now many researchers believe that the permeability change is associated with an increase in temperature induced blood flow.

In spite of reports to the contrary, no validated research on memory and cognitive functioning in humans exposed to MP emissions at low levels indicates an adverse human health effect. The human acute studies' positive results on learning and memory from MP exposure are put into perspective by the failed replication of Koivisto et al. [2000a] in a subsequent study with improved methodology by Haarala et al. [2003]. Although there are reports of speeding up of reaction times due to exposure in tasks requiring attention and short term memory, the effects are seen only in a small number of tasks used; most of the tasks have found no effect. Additional research is needed to further evaluate the effects of RF exposure on working memory and cognition.

Perhaps the most interesting and more complete areas of study of RF effects on the central nervous system are the reported effects of MW on brain neurochemistry and interactions with drugs. Some interactions would have to rely on BBB alteration to allow passage of high molecular compounds into the brain. At high SAR levels, it is possible that the MW exposure can enhance the passage of compounds across the BBB and blood–cerebrospinal fluid barrier. However, at low power densities, it is questionable that the BBB permeability is changed during exposure. Studies that have examined the neurochemistry of the brain or studied interactions with drugs have discovered that distribution of absorbed RF energy within the body and brain is very complicated. The change in local blood flow due to different SAR distributions might alter the drug distribution in the brain. Some effects are reported to occur after pulsed exposure but not CW exposures [Lai, 1992]. The auditory system is very sensitive to pulsed MW exposure. This sensory input can affect the brain functions and alter the actions of psychoactive drugs.

Thermal mechanisms seem to explain some effects of MW on neurochemistry. Studies at these levels have observed effects on norepinephrine, dopamine, and serotonin. Other studies report low level effects where thermal mechanisms cannot explain the results. For example, the hypothesis that low level MW exposure acts as a stressor and activates cholinergic systems and endogenous opioid systems has generated much research over the past two decades. Studies of low level MW effects on anterior pituitary hormones and melatonin have been unsuccessful in finding reliable changes.

Of the studies that evaluate MW effects on the peripheral nervous system and isolated tissue, the work

of Tattersall et al. [2001] is most interesting. They have shown that 700 MHz (CW) exposure at field intensities in the range of 25.2–71 V/m produces effects on evoked and spontaneous potentials in rat hippocampal slices. Their work has shown so far that these effects are not associated with a temperature increase and temperature changes of up to 1 °C failed to reproduce such potentiation. Previous studies have shown that isolated tissues can be affected by MW exposure, but many of the reported changes were temperature related. Replication of such effects seem of paramount importance to our understanding of RF effects on the nervous system.

Numerous reports of MP use producing subjective symptoms, such as headache and perceptions of warmth, have been evaluated several times with field surveys. While the association between nervous system symptoms and MP exposure in each of these studies is seemingly significant, many factors could influence the outcome and all studies lack strength in providing a cause and effect relationship. There are individuals who report EHS and who believe they are influenced by electric and magnetic fields from a variety of sources. They report symptoms that are related to the nervous system such as fatigue, stress, and sleep disturbances. However, in controlled provocation experiments none of the test subjects could distinguish a real RF exposure from sham exposures. Until other possible causes of the symptoms are ruled out, such as mycotoxins, it will be difficult to prove that low level RF is responsible.

Overall, in reviewing the scientific literature, which evaluates the effects of MW on electrical activity, the BBB, tissue morphology, drug interactions, and neurochemistry of the CNS, one finds that the outcomes of the various studies have been inconsistent and comparison between individual studies difficult. Vander Vorst and Duhamel [1996] reviewed the nervous system and RF literature and also concluded that the diverse methods and experimental designs prevent formation of definite conclusions concerning health effects from RF exposure. The long standing issue of whether CW or pulsed RF is more effective for biological results is still controversial. Likewise, many nervous system effects have been reported that can best be explained by thermal mechanisms. Some reports of biological effects that cannot be explained by thermal mechanisms are in the scientific literature. These will require much more research to fully understand the mechanisms involved. Regardless of the mechanism, reports of effects that are at or below current recommended safety guidelines deserve rapid evaluation.

One recommendation is that investigators pursue replication both within a laboratory and across laboratories. It is recommended that several laboratories simultaneously replicate an important identical paradigm, including time course and dose effect features. Replication is an important component of any successful experiment.

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