RECENT ADVANCES IN RESEARCH ON RADIOFREQUENCY FIELDS AND HEALTH: 2001–2003

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ABSTRACT

The widespread use of wireless telecommunications devices, particularly mobile phones, has resulted in increased human exposure to radiofrequency (RF) fields. Although national and international agencies have established safety guidelines for exposure to RF fields, concerns remain about the potential for adverse health outcomes to occur in relation to RF field exposure. The extensive literature on RF fields and health has been reviewed by a number of authorities, including the Royal Society of Canada (1999), the American Cancer Society (2001), the European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment (2001), the British Medical Association (2001), the Swedish Radiation Protection Authority (2002), and the Health Council of the Netherlands (2002). This report provides an update on recent research results on the potential health risks of RF fields since the publication of the Royal Society of Canada report in 1999 (*J. Toxicol. Env. Heal.,* B4, 1–143) and our previous 2001 update (*J. Toxicol. Env. Heal.,* B4, 145–149), covering the period 2001–2003. The present report examines new data on dosimetry and exposure assessment, thermoregulation, biological effects such as enzyme induction, and toxicological effects, including genotoxicity, carcinogenicity, and testicular and reproductive outcomes. Epidemiological studies of mobile phone users and occupationally exposed populations are examined, along with human and animal studies of neurological and behavioural effects. All of the authoritative reviews completed within the last two years have concluded that there is no clear evidence of adverse health effects associated with RF fields. At the same time, these same reviews support the need for further research to clarify the possible associations between RF fields and adverse health outcomes that have appeared in some reports. The results of the ongoing WHO study of mobile phones will provide important new information in this regard.

INTRODUCTION

The use of radiofrequency (RF) field emitting devices such as mobile phones, microwave ovens and RF heaters, base stations, radar installations, telecommunications and broadcast facilities has led to widespread human exposure to RF fields. The remarkable growth of this relatively new technology especially mobile phones and base stations has raised public concerns about possible associations between RF fields and adverse health outcomes, including cancer. To date, there is limited information on the health risks stemming from the use of such equipment. As more products and services are developed and used in everyday applications, the potential for human exposure to RF fields is likely to increase and consequently public concerns will continue.

The Royal Society of Canada’s Expert Panel on Potential Health Risks from Wireless Telecommunication Devices conducted a detailed review of potential health risks of RF fields from wireless telecommunication devices (Royal Society of Canada, 1999; Krewski et al., 2001a). Subsequent research reported in the literature during the period 1999–2000 was then reviewed by Krewski et al. (2001b). This article is a continuation of the effort to review the literature on RF fields and health, specifically for the period 2001–2003.

DOSIMETRY AND EXPOSURE ASSESSMENT

Dosimetry involves measuring the dose of radiation emitted by a particular source, and includes the evaluation of both incident and internal fields. Internal fields and currents are responsible for interactions with living systems, regardless of whether these interactions are thermal or non–thermal. Internal and incident electromagnetic (EM) fields can be quite different, depending on the size and shape of the object, its electrical properties, its orientation with respect to the incident fields, and its operating frequency.

Dosimetry involves the measurement or determination by calculation of the internal fields, induced current density, or specific absorption rate (SAR) distributions in objects like models (phantoms), animals, humans, or even parts of human body exposed to RF fields. Because of the complexity and non–homogeneous character of biological tissues, it is difficult to fully characterize the propagation of

RF fields in human body.

Mobile Phones

A mobile handset represents a significant source of RF field exposure, because of the presence of the phone–transmitting antenna close to head, neck, and hand of the user. Model–based predictions of the SAR associated with mobile phones are now required to comply with established exposure guidelines (1.6 W/kg or 2 W/kg) for the head and neck area. Mobile phone manufacturers are continually interested in reducing SAR as much as possible, not only to reduce exposure to RF fields, but also to increase the battery life.

The local peak SAR levels inside the human head differ depending on many factors such as the antenna type, antenna radiation efficiency, antenna inclination with the head, distance of antenna from head, effect of the hand holding the handset, and the structural accuracy and resolution of the head model. A number of dosimetric studies have been performed for calculating or measuring power absorbed in phantoms simulating human heads exposed to RF fields. Recently, Van de Kamer and Lagendijk (2002) calculated SAR from dipole antennas radiating 250 mW at 900 MHz. Some SAR values exceeded the limits–commonly called “maximum permissible exposure” (MPE) values, while other values were below the MPE values. Moneda et al. (2003) verified by the means of numerical calculation that the higher the frequency the more superficial is the absorption. The numerical application manifests that the eyes, despite their small volume, absorb considerable amounts of the incident RF field, especially when the antenna is in front of the head, which is the most typical configuration related to use of mobile phones. Another important issue which was raised by the authors is the enhancement of the hot spots near the center of the brain as the size of the head is reduced, which points to potential hazards to children using mobile phones.

To calculate temperature rise in the human head exposed to RF fields at 1.5 GHz at a density of 1 mW/cm^2, Yano, et al. (2001) developed a realistic adult head model and an infant size model by reducing the adult model. In the adult model, the maximum rise of temperature was reached in the eyeballs (0.07 ^oC), while in the infant model, the maximum rise of temperature occurred in the muscle (0.0058 ^oC). The tissue average temperature rise was higher in the infant model than in the adult model except for the eyeballs. In particular, the average value of the temperature rise in the brain tissue was lower than the peak value by almost one order of magnitude and was three times higher than the average value in the adult. The reported results were attributed to the hot spots of SAR as a heat source generated inside the head.

Base Stations

The rapid growth of the cellular telecommunications industry has resulted in the installation of large networks of base transceiver stations (BTSs), which may be mounted on freestanding towers, rooftops, or the sides of buildings. Measurements near typical BTSs have mostly shown that exposure levels are well within the widely promulgated guidelines (Silvi et al., 2001; Anglesio et al., 2001; Cooper et al., 2002).

A report by the Advisory Group on Non–Ionizing Radiation of the National Radiological Protection Board (NRPB, 2001) giving advice on possible health effects of terrestrial trunked radio (TETRA) concluded that: "Although areas of uncertainty remain about the biological effects of low level RF radiation in general, including modulated signals, current evidence suggests that it is unlikely that the special features of the signals from TETRA mobile terminals and repeaters pose a hazard to health." In an expert group report to the Director General of Health of France, Zmirou (2001) noted that personal exposures in the vicinity of base stations were low, and stated that "in view of the exposure levels observed, the expert group does not back the hypothesis that there is a health risk for populations living in the vicinity of base stations."

Environmental Levels

Hondou (2002) found that when hundreds of mobile phones emit radiation, their total power is comparable to a microwave oven or a satellite broadcasting station and this level can reach the reference level for general public exposure recommended by the International Commission on Non–Ionizing Radiation Protection (ICNIRP, 1998). This is caused by the fundamental properties of EM fields, namely, reflection and additivity. However, Toropainen (2003) applied radio–engineering principles to estimate the power density and SAR levels versus the number of mobile phones in screened environments occupied by humans. The author concluded that it is unlikely that exposure levels are exceeding the safe limits recommended by the ICNIRP due to multiple mobile phones users in train, elevators, cars or similar environments.

Magnetic Resonance (MR) Systems

Magnetic resonance (MR) systems are used in diagnostic medicine and display images in a format similar to computed tomography. Many safety issues regarding these systems, however, remain as possible concerns. A number of computational reports have predicted the possibility of high SAR levels at high frequencies and formation of regions of high RF intensity (hot spots) inside the human body at higher field strengths (Collins and Smith, 2001; Kangarlu et al., 2003).

THERMOREGULATION

Thermoregulation, or the maintenance of a fairly steady body temperature even under a variety of external conditions, is important to humans because each body has a preferred temperature at which functioning is optimal. These external conditions can include changes in temperature, vapour pressure, air velocity, exposure to radiation including RF fields, and insulation among other factors that affect the temperature of the skin. Previously, Adair et al. (1999) measured thermoregulatory responses of heat production and heat loss in adult volunteers. Subsequently, Adair et al. (2001) exposed two different groups of volunteers to 2450 MHz continuous wave (CW) (two females, five males) and pulsed wave (PW) (65 seconds pulse width, 10^4 pulse per second (pps); three females, three males) RF fields. They measured thermo-physiological responses of heat production and heat loss under a standardized protocol (30-minute baseline, 45 minute-RF or sham exposure, 10-minute baseline), conducted in three ambient temperatures (24, 28, and 31°C). At each temperature, average power density studied were 0, 27, and 35 mW/cm^2 (SAR = 0, 5.94, and 7.7 W/kg). Mean data for each group showed minimal changes in core temperature and metabolic heat production for all test conditions and no reliable differences between CW and PW exposure. Local skin temperatures showed similar trends for CW and PW exposure that were power density–dependent; only the skin temperature of the upper back (facing the antenna) showed a reliably greater increase during PW exposure than during CW exposure. Local sweat rate and skin blood flow were both temperature and power density–dependent and showed greater variability than other measures between CW and PW exposures; this variability was attributable primarily to the characteristics of the two subject groups. Similar results were obtained by Adair et al. (2003).

Recently, Adair and Black (2003) reviewed the current literature concerned with physiological thermoregulatory responses of humans in the presence of RF fields. They stated: "The conclusion is inescapable that humans demonstrate far superior thermoregulatory ability over other tested organisms during RF exposure at, or even above current human exposure guidelines."

BIOLOGICAL EFFECTS

Ornithine Decarboxylase (ODC)

ODC is an important enzyme for the role it plays in regulating cell growth through synthesis of polyamines necessary for protein and deoxyribonucleic (DNA) synthesis. ODC is an enzyme activated during carcinogenesis. Increased ODC activity is an indication for cancer.

Stagg et al. (2001) exposed immobilized Fischer 344 rats in a dose–dependent manner to pulse–modulated (11 packets/second) digital RF fields at 1.6 GHz in accordance with the Iridium protocol. When RF–exposed and sham–exposed (immobilized) animals were compared, no differences were seen in core body temperature, corticosterone or adrenocorticotrophic hormone (ACTH) that could be attributed to near–field RF exposure. Levels of ODC, Fos and Jun mRNA were also monitored in brains of animals exposed to the RF field for 2 hours, and they showed no differences from sham–exposed (loose–tube immobilized) animals that were exposed to RF fields. The authors concluded that the pulse–modulated Iridium signal at SARs up to 5 W/kg is incapable of altering the stress–related responses.

Paulraj and Behari (2002), however, described the effect of low level CW microwaves (2.45 GHz) on developing rat brain. Some 35-day-old Wistar rats were used for this study. The animals were exposed 2 hours/day for 35 days at a power density of 0.34 mW/cm^2 (SAR = 0.1 W/kg) in a specially made anechoic chamber. A significant increase in calcium ion efflux and ODC activity was observed in the exposed group as compared to the control. Correspondingly, a significant decrease in the calcium-dependent protein kinase activity was observed. The results indicated that this type of radiation affects the membrane bound enzymes, which are associated with cell proliferation and differentiation, thereby pointing out its possible role as a tumor promoter.

Intracellular Calcium

In a study designed to test whether exposure to simulated global system for mobile communication (GSM) phone signals influences the concentration of calcium or calcium signalling patterns in single cells, Cranfield et al. (2001) estimated the intracellular calcium concentration ($[Ca^{2+}]_i$) in the human lymphocyte cell line, Jurkat, exposed to 915 MHz at 2 W/kg RF fields. The results indicated that there is no clear indication that RF emission from mobile phones are associated with any changes in calcium levels or calcium signalling in lymphocytes, although an alteration in the frequency of calcium oscillations was noted in activated cells exposed to pulsed wave RF. On the other hand, Guisasola et al. (2002) showed that 64 MHz RF field exposure, associated with turbo spin echo MR imaging resulted in a significant increase in $[Ca^{2+}]_i$ in human embryonic lung cells, L–132. However, exposure to MR related static and gradient fields showed no effect on $[Ca^{2+}]_i$.

Besides studies investigating the effects of exposure from RF fields there have been a number of reports evaluating the effect on intracellular calcium and cell calcium signalling when exposure is to extremely low frequency (ELF) magnetic fields. We summarize these studies here because there have been suggestions that it is the ELF modulation of the RF fields which may be responsible for non–thermal biological effects.

Experiments assessed whether long term exposure to 50 Hz pulsed EM field with a peak magnetic field of 3 millitesla (mT) can alter the dynamics of intracellular calcium in human astrocytoma cells. Pessina et al. (2001) found that a 50–Hz square wave exposure of astrocytoma cells resulted in either a decrease or increase in calcium signalling depending on the stimulus used. (Caffeine and unstimulated cells showed an increase while substance P and substance P+ caffeine showed a decrease in Ca^{2+} response). This study suggests that magnetic fields act either on intracellular Ca^{2+} stores or on the plasma membrane. Moreover, EM fields that affected intracellular calcium did not cause cell proliferation or cell death.

Ikehara et al. (2002) investigated possible mechanisms for the effects of a 1.51 T pulsed field associated with a transcranial magnetic stimulator on cultured bovine adrenal chromaffin cells. Previously, this group observed a suppression of $[Ca^{2+}]_i$ signalling pathway when cells were in a Ca^{2+} free medium (Ikehara et al., 1998). This more recent study revealed that the magnetic field exposure inhibits Ca^{2+} release from intracellular Ca^{2+} stores but the Ca^{2+} flux across the plasma membrane did not change.

Spadaro and Bergstrom (2002) showed an increase in Ca^{2+} uptake in the rat calvarial bone after 2 hour exposure to a pulse 1 mT magnetic field (5 milliseconds (ms) burst, 20 burst train, at 15 Hz). These effects were observed immediately after exposure and 24 hours later, but not after 48 hours.

Obo et al. (2002) found that calcium flux across the plasma membrane of PC–12D cells from rat pheochromacytoma did not change when parametric magnetic field exposure conditions were used (static fields < 0.07 mT, frequencies 14 to 50 Hz with amplitudes 0.015 to 0.15 mT). Another study examining the effects of combined static and oscillating magnetic fields, as well as other frequencies, was recently performed by Madec et al. (2003). This group found no evidence of alterations in calcium oscillation patterns or frequencies in mouse islets of Langerhans exposed to either 1 mT static, various sinusoidal ELF frequencies at 0.1 and 1 mT, or "cyclotron resonant" conditions.

McCreary et al. (2002) have done an extensive set of experiments exposing a human transformed cell line (Jurkat) to static 78–microtesla (μT), oscillating (60 Hz, 100 μT peak sinusoidal), and the parallel combination of static and oscillating EM fields. This combination has been proposed to couple to a metal ion in a protein well by two prominent theoretical groups (Lednev et al., 1991; Blanchard et al., 1994). McCreary's work indicates that the effect on intracellular calcium is probably small and the sensitivity of cells to magnetic fields may be dependent on the cell cycle. Using similar combined fields, Bauréus Koch et al. (2003) studied calcium efflux in highly purified spinach plasma membrane vesicles. Static magnetic fields ranging from 27 to 37 μT and time varying magnetic fields with frequencies between 7 and 72 Hz and peak amplitudes between 13 and 114 μT were used. They showed that such fields can affect the Ca^{2+} channel protein in the cell membrane and the results were in agreement with the theoretical model proposed by Blanchard et al. (1994).

Yamaguchi et al. (2002) found that Mc 3T3–E1 pre–osteoblast cells and ROS 17/2.8 differentiated osteoblast cells did not alter $[Ca^{2+}]_i$ when exposed to 0–1.25 mT, 60 Hz sinusoidal magnetic fields. This is despite observed decreases in intercellular communication through gap junctions. Decreased gap junction intercellular communication in synovial fibroblasts exposed to 60 Hz electric fields was reported recently by Marino et al. (2003a). In this study, a significant increase in Ca^{2+} influx was observed and the group suggested that the alteration in gap junction communication was dependent on Ca^{2+} influx rather than changes in membrane potential.

Craviso et al. (2002) studied $[Ca^{2+}]_i$ in isolated bovine adrenal chromaffin cells exposed to 60 Hz magnetic fields at 0.01, 0.1, 1.0, 1.4, and 2.0 mT. With respect to number of cells exhibiting transients, the number and types of transients, no significant effects were seen. However, the percentage of cells that responded to a nicotinic cholinergic receptor agonist was significantly higher after one day exposure compared to sham or unexposed cultures. This provides evidence that plasma membrane nicotinic receptors may be affected by the exposure.

In addition to magnetic field effects on $[Ca^{2+}]_i$, other reported effects of ELF exposure have been shown to depend on calcium. For example, Zhou et al. (2002) found that 0.1 mT, 50 Hz magnetic field exposure induced an increase in cyclic–AMP response element binding protein binding DNA in HL60 cells was dependent on both extra– and intracellular calcium.

Tonini et al. (2001) found that the effects of 50 Hz magnetic field (120 and 240 μT) exposure on chemically induced differentiation of neuroblastoma/glioma culture cells, NG108–15, was dependent on the extracellular calcium concentration.

Cell Proliferation

D'Ambrosio et al. (2002) exposed human peripheral blood cultures to 1.748 GHz, either CW, or phase only modulated wave (Gaussian minimum shift keying, GMSK). SAR used (5 W/kg) was higher than that occurring in the head of mobile phone users. No changes were found in cell proliferation kinetics after exposure to either CW or GMSK fields.

Aldinucci et al. (2003) investigated whether static EM fields at a flux density of 4.75 T, generated by a nuclear magnetic resonance (NMR) apparatus, could promote movements of Ca^{2+}, cell proliferation, and the eventual production of proinflammatory cytokines in human peripheral blood mononuclear cells (PBMC) as well as in Jurkat cells, after exposure to the field for 1 hour. The same study was also performed after activation of cells with 5 mg/ml phytohaemagglutinin (PHA). The results clearly demonstrate that static NMR 4.75 T exposure has neither proliferative, nor activating, nor proinflammatory effects on both normal and PHA activated PBMC. Exposure of Jurkat cells significantly decreased the proliferation. Moreover, the concentration of interleukin-1â, interleukin-2, interleukin-6, interferon, and tumour necrosis factor á (TNFá) remained unvaried in exposed cells.

Blood Brain Barrier (BBB)

RF–induced breakdown of the BBB have been studied either alone or in combination with magnetic fields. Leszczynski et al. (2002) reported that heat shock protein 27 (hsp 27) was transiently increased by non–thermal exposure to a 900–MHz GSM mobile phone signal. Based on the known functions of hsp 27, it was proposed that this might cause an increase in BBB permeability through stabilization of endothelial cell stress fibers. Other studies have not found RF–induced disruption of the BBB (Finnie et al., 2001, 2002). Most of the studies conclude that high–intensity RF fields are required to alter the permeability of the BBB. Recently, Salford et al. (2003) have shown that extremely low doses of GSM radiation can cause brain damage in rats. The authors reported nerve damage following a single two–hour exposure at a SAR of 2 mW/kg. They showed that RF energy can impair the BBB, but they added that the chemicals that leak through the BBB probably damage neurons in the cortex, the hippocampus and the basal ganglia of the brain. The cortex is close to the surface of the skull, while the basal ganglia are much deeper.

Recently, D'Andrea et al. (2003a) reviewed this subject and concluded: “Effects of RF exposure on the 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.”

Melatonin

It has been suggested that RF fields may have a cancer-promoting effect by altering circadian rhythms of pineal activity and melatonin release. RF field effect on melatonin has been conducted in several human and animal studies.

Human studies. Griefhan et al. (2001) exposed young healthy male volunteers (16–22 years) to ELF fields (16.7 Hz). The exposure did not reveal any alteration in salivary melatonin production. The authors concluded that the results of their study, together with other published investigations using that particular field, lead to the hypothesis that melatonin production suppression in humans most likely, occur, only after repeated exposure to intermittent fields.

Radon et al. (2001) conducted a study to evaluate the effects of RF fields used in GSM systems on salivary melatonin, neopterin, and immunoglobulin A (sIgA) levels during and after several hours of exposure. Eight healthy student were exposed to 900 MHz pulsed with 217 Hz (average power flux density of $1 W/m^2$). The results obtained showed that the salivary concentrations of melatonin, cortisol, neoptrin, and (sIgA) did not differ significantly between exposure and sham exposure.

However, Burch et al. (2002) conducted a study of male electric utility workers. Personal 60–Hz magnetic field (MF) and ambient light exposures were characterized on the same days using EMDEX II meters. A repeated measures analysis was used to assess the effects of cellular telephone use, alone and combined with MF exposures, after adjustment for age, participation month and light exposure. They reported that cellular phone use of greater than 25 minutes per day was associated with a drop in melatonin. This effect, however, was seen only on the third day of the study. The authors concluded that prolonged use of cellular phones may lead to reduced melatonin production, and elevated 60–Hz MF exposures may potentiate the effect.

In another small study of 9 healthy males aged 19-29 years, Bortkiewicz et al. (2002) found no change in melatonin excretion due to exposure from a cellular phone of one hour (900 MHz, pulsed with 217 Hz, SAR = 1.23 W/kg).

Animal studies. Tripp et al. (2003) administered circularly polarised 50 Hz magnetic fields to isolated pineals in highly controlled conditions. Melatonin release from isolated Wistar rat pineal glands, dissected 2 hours after light onset ZT 2, was measured in a flow through culture system, during and after exposure to a 4–hour magnetic field similar in nature and magnitude to that produced in extremely close proximity to a high voltage power line (500 μT, 50 Hz circularly polarised). No significant alterations in pineal melatonin release were caused by exposure to the magnetic field when compared to sham exposure exposed to < 1 μT.

Bakos et al. (2003) exposed seventy–two adult male Wistar rats in six independent experiments, three of which were done with 900 MHz (100 mW/cm^2) and the other three with 1800 MHz (20 mW/cm^2) GSM RF radiation modulated with 218 Hz. The exposures were performed in a gigahertz transverse EM mode (GTEM) cell. The animals were exposed for 2 hours between 8:00 AM and noon daily during a 14 day exposure period. The urine of rats was collected from 12:00 AM to 8:00 AM, collecting from exposed and control animal groups on alternate days. Urinary 6–sulfatoxymelatonin (6SM) concentration was measured by (125) I radioimmunoassay and was referred to creatinine. Statistically significant changes in the 6SM excretion of exposed rats (n = 18) compared to control group (n = 18) were not found either at 900 or 1800 MHz.

Review study. In a review of the effects of RF radiation on the endocrine system, Black and Heynick (2003) concluded that: "There is limited evidence that indicates no interaction between RF radiation and the pineal gland."

Immune System

Radon et al. (2001) found that mobile phone RF radiation had no effect on immune function in on eight healthy young men. The men were exposed to 900 MHz fields, pulsed with 217 Hz, pulse width 217 μs. An antenna was positioned 10 cm behind the subject's head. The power-flux density was approximately 1 W/m^2, and the maximum local SAR in the head (averaged over 10g tissue) was 0.025 W/kg. The study was designed to assess the effects of the RF fields on salivary levels of melatonin, cortisol, neopterin, and IgA. Neopterin and IgA are substances that are part of the immune system.

Gatta et al. (2003) found that 900 MHz GSM-modulated radiation for 1, 2, and 4 weeks (2 h/day) in a TEM cell to a SAR of 1 or 2 W/kg had no substantial effects on immune function in mice.

Black and Heynick (2003) reviewed the subject and concluded: "Lifetime studies of RF radiation exposed animals show no cumulative adverse effects in their endocrine, hematological, or immune systems."

Cardiovascular Diseases

Braune et al. (1998) reported that exposure of human volunteers to RF fields of mobile phones (GSM 900-MHz, 2-W, 217-Hz frame repetition rate) increased the sympathetic efferent activity with increases in the resting blood pressure between 5-10 mm Hg. However, Braune et al. (2002) repeated their study and summarized that RF fields had no effect on the outcomes. They claimed that their 1998 finding of increased blood pressure in mobile phone users was due to an artifact in the design of the original study.

Black and Heynick (2003) reviewed the subject and concluded: "Cardiovascular tissue is not directly affected adversely in the absence of significant radiofrequency electromagnetic fields (RFEMF) heating or electric currents. The regulation of blood pressure is not influenced by ultra high frequency (UHF) RFEMF at levels commonly encountered in the use of mobile communication devices."

TOXICOLOGICAL EFFECTS

Genotoxicity

A number of laboratory experiments have been conducted to assess possible genotoxic effects of a broad range of different RF frequencies at a variety of levels of biological complexity. Many of the experiments found no evidence for any direct genotoxic or mutagenic effects of RF fields at different power densities. These include DNA damage (Li et al., 2001; McNamee et al., 2002a,b), damage to chromosomes (Vijayalaxmi et al., 2001a,b; Gadhia et al. 2003), induction of sister chromatid exchange (SCE) (Maes et al., 2001; Gadhia et al. 2003), induction of micronuclei (Vijayalaxmi et al., 2001a,b; Bisht et al., 2002; McNamee et al., 2002a,b; Zeni et al., 2003; Koyama et al., 2003), cell transformation (Roti Roti et al., 2001), and mutation in Big Blue mouse neural tissue (Takahashi et al., 2002).

However, as a part of comprehensive investigation of the potential genotoxicity of RF signals emitted by several types of mobile phones, Tice et al. (2002) demonstrated that, under protracted exposure, RF fields from mobile phones at an average SAR of at least 5 W/kg can cause strand breaks or other damage to DNA, as well as chromosomal damage in human lymphocytes. The signals studied included voice modulated 837 MHz generated by an analog signal generator or a time division multiple access (TDMA) mobile phone, unmodulated 837–MHz from a code division multiple access

(CDMA) mobile phone, and voice modulated 1909.8 MHz from a personal communication system (PCS) mobile phone via a GSM system.

Similar findings were reported by d'Ambrosio et al. (2002) while irradiating diluted blood with 1748 MHz either as a CW or a GMSK signal for 15 minutes at 5 W/kg. This study was conducted without the concurrent TDMA amplitude modulation used in GSM 1800 mobile phones. Mashevich et al. (2003) also reported genotoxic effects when radiating human lymphocytes to continuous 830 MHz RF energy at SAR in the range 1.6–8.8 W/kg for 72 hours.

Sykes et al. (2001) exposed a group of pKZ1 mice to pulsed 900 MHz RF radiation (4 W/kg) daily for 30 minutes. The exposure employed plane–wave field with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms for 1, 5, 25 days. Three days after the last exposure, spleen sections were screened for DNA inversion events. No significant differences were observed between the control and the exposed groups in the 1–, and 5–day exposure groups. In a 25–day exposure group, they observed a significant reduction in the inversions below the spontaneous frequency. The observation suggest that exposure to RF field can lead to a perturbation in the recombination frequency which may have implications for recombination repair of DNA.

Zhang et al. (2002) exposed human blood cells to 2450 MHz RF radiation for 2 hours at 5 mW/cm^2 and/or a chemical carcinogen. The RF radiation alone was not genotoxic (DNA strand breaks and micronucleus assay), but was reported to enhance the genotoxic effects of the chemical carcinogen. There is insufficient information about the RF exposure conditions to exclude heat-induced effects.

Recently, Meltz (2003) reviewed the *in vitro* literature relevant to the issue of the possible induction of toxicity, genotoxicity, and transformation of mammalian cells due to RF exposure. According to the author, the review was conducted from the perspective of technical merit and also biological consistency, especially with regard to those publications reporting a positive effect. The reviewer concludes: “The weight of evidence available indicates that, for a variety of frequencies and modulations with both short and long exposure times, at exposure levels that do not (or in some instances do) heat the biological sample such that there is a measurable increase in temperature, RF exposure does not induce (a) DNA strand breaks, (b) chromosome aberrations, (c) sister chromatid exchanges (SCEs), (d) DNA repair synthesis, (e) phenotypic mutation, or (f) transformation (cancer–like changes).”

Carcinogenicity

As RF exposure is not considered to be directly carcinogenic, research is aimed towards its possible promotional and co–promotional effects. Three studies have suggested that high levels of exposure to RF fields may be associated with an increased tumour incidence in animals (Repacholi et al., 1997; Trosic et al., 2002, Zhang et al., 2002). However, Utteridge et al. (2002) could not replicate the increase in lymphoma in either normal mice or in the same lymphoma prone mice reported by Repacholi et al. (1997). Other studies have shown no increase in tumour development rates (Zook and Simmens, 2001; Mason et al. 2001; Jauchem et al., 2001; Heikkinen et al., 2001; Imaida et al. 2001; Bartsch et al., 2002; Vijayalaxmi, 2003; Heikkinen et al. 2003; Anane et al., 2003; La Regina et al., 2003) at moderate levels of exposure to RF fields.

Repeated exposure to mobile phone radiation was found to act as a repetitive stress leading to continuous expression of Hsps in exposed cells and tissues, which in turn affects their normal regulation, and cancer results. This hypothesis which was presented by French et al. (2001) provides the possibility of a direct association between mobile phone use and cancer. The authors pointed out that the cellular response is characterized by the formation of Hsps, which protect cells against damage produced by stress. They cite evidence that Hsps can also play a role in cancer induction or promotion, though they state that there is debate as to whether the association with cancer is causal or correlative. They suggest that recurrent exposure to frequent mobile phone use could lead to chronic expression of Hsps in the brain tissue of users and that this in turn might induce or promote cancer.

Di Carlo et al. (2002) exposed chicken embryos to ELF–EM fields (8 μT) continuously for 4 days, or to ELF or RF exposures (3.5 mW incident power) repeated daily for 4 days. Several of the exposure protocols yielded embryos that had statistically significant decrease in protection against hypoxic stress. Following 4 days of ELF–EM exposure, Hsp 70 levels declined by 27% as compared to controls. The superposition of ELF–EM noise inhibited hypoxia de–protection caused by long term, continuous ELF fields or daily, RF exposures. The authors concluded that this EM–induced decrease in HSP70 levels and resulting decline in cytoprotection suggests a mechanism by which daily exposure could enhance the risk of cancer and other adverse health outcomes.

Shallom et al. (2002) exposed chick embryos to 915 MHz radiation at approximate SARs of 1.5 and 2.5 W/kg in different experiments. Levels of Hsp 70 were found to increase by approximately 30% compared to controls, with peak expression occurring by 3 hours from the start of exposure. Final temperatures, measured with thermocouples situated next to the embryos, did not exceed 38.8ºC. The authors did not feel that this temperature was the cause of the increased production of Hsp 70, since heating of the chick embryos to 39 ºC did not produce an increase in Hsp 70 levels. The authors concluded that their study provides support for the hypothesis that "athermal EM field exposures induce Hsp 70 expression." This finding is supported by another study (Kwee et al., 2001). Moreover, De Pomerai et al. (2003) emphasized that RF radiation does not produce harmful effects on humans. In fact, they say that it is conceivable that moderate RF radiation might even prove beneficial. They feel, however, that their latest experiments provide further evidence that RF field can produce non–thermal biological effects. This group has previously shown that RF radiation can induce the formation of Hsps in the C. Elegans nematode (De Pomerai et al., 2000).

Recently, Heynick et al. (2003) reviewed studies on cancer and related effects from exposure to EM fields in the nominal frequency range of 3 kHz to 300 GHz. They concluded: "The preponderance of published epidemiologic and experimental findings do not support the supposition that *in vivo* or *in vitro* exposures to such fields are carcinogenic."

Testicular Function and Teratogenicity

Bol'shakov et al. (2002) studied the combined effect of 460–MHz RF radiation and increased (up to 40^{o}C) temperature on Drosophila embryos of definite age. The results of the study indicated that RF radiation did not produce any effect on development of the Drosophila.

Elbetieha et al. (2002) exposed male and female mice to 50–Hz magnetic fields for extended periods. No effect was seen on the weight of the testes, seminal vesicules, preputial gland or body weights for males. Body and uterine weights were not affected in females; but ovarian weight was significantly increased. It was concluded that exposure of male and female mice to low frequency magnetic field had no adverse effects on fertility and reproduction in mice.

Ohnishi et al. (2002) found that magnetic fields (50–Hz, 0.5 mT and 5.0 mT, for 9 and 2 weeks) have no major effects on reproduction and development in mice, and do not support the association of EM exposure with adverse reproductive effects suggested in the epidemiological literatures.

Dasdag et al. (2003) investigated the effect of RF radiation emitted from cellular phones on the lipid composition, malondialdehyde concentration, p53 immune reactivity, sperm count, morphology, histological structure of testes, and on rectal temperature of rats. For 250 mW radiated power, the whole body average SAR was 0.52 W/kg and 1 g averaged peak SAR was 3.13 W/kg. The results indicated that there was no statistically significant alteration in any of the assayed end points. Hence, this study found no evidence suggesting an adverse effect of mobile phone exposure on measures of testicular function or structure.

EPIDEMIOLOGICAL STUDIES

At the time of release of the Royal Society of Canada report in 1999 (Royal Society of Canada, 1999), the epidemiologic research was considered to be inadequate to provide evidence as to whether exposure to mobile phones or RF fields carried an increased risk of cancer or other detrimental health effects. Several epidemiological studies published in 1999 and 2000 were reviewed in an update to that report published in this Journal (Krewski et al., 2001a,b). The following review describes the studies published since that time, including several case–control and cohort investigations of mobile phone users, and updates to previous cohort investigations.

Studies of Mobile Phone Users

Muscat et al. (2000) carried out a case–control study of brain cancer in northeastern US, involving 469 cases diagnosed between 1994 and 1998, and 422 hospital–based controls. Self–reported exposure included information on frequency, duration, and laterality of use of cellular phones, and information on potential modifiers. Median monthly hours of use was 2.5 hours for cases and 2.2 hours for controls. Mean duration of use was 2.8 years for cases and 2.7 years for controls. Adjusted risk of brain cancer with regular or ever use of a cellular phone in this study group was 0.85 (95% CI = 0.6–1.2). No relationship of brain cancer risk and duration or frequency of use of a cellular phone was observed in this study when the odds ratio (OR) for infrequent users = 1.0 or when OR for frequent users = 0.7) (p value for duration of use = 0.54). Neither was there any relationship of risk with brain cancer subtype, except for neuroepitheliomatous cancer (OR = 2.1; 95% CI, 0.9–4.7), based on 35 cases, 10 of which were located in the temporal lobe. Laterality of phone use was not associated with location of temporal lobe tumours.

Another case–control study of brain tumours was carried out in the US, involving 782 cases of intracranial tumours of the nervous system identified between 1994 and 1998, and 799 hospital–based controls, by Inskip et al. (2001). Use of mobile phones was by self–report of type of mobile phone, start and end of time of use, duration of "regular" use, frequency of use, and hand used to hold the phone. Results were adjusted for socioeconomic variables and history of medical exposure to ionizing radiation. No association was observed between ever use or regular use of a cell phone and risk of any of the types of brain tumour (OR = 1.0 overall; 0.7 for high–exposed group); nor was a higher risk identified for those with longer use, increasing duration or frequency or total cumulative use of cellular phones. No association was seen between laterality of tumour and laterality of phone use. Both of these studies were unable to assess risks of long–term use and use of the newer digital phones. Because both studies were of case–control design, there is also a potential for bias due to non–representative control selection and incomplete participation rates, and potential for error in self–reports of phone use.

Johansen et al. (2001) has reported on the cancer experience of a cohort of over 420,000 private cellular phone subscribers in Denmark from 1982 to 1995. Overall, 3391 cancers were identified through the Danish Cancer Registry among these subscribers. The cohort had a significantly decreased standardized cancer incidence ratio (SIR) of 0.89, mainly accounted for by decreased risk of cancer of the lung and other smoking–related cancers. No increased risk was observed for cancers of the brain or nervous system (SIR = 0.97, 95% CI, 0.78–1.21), for salivary gland cancer (SIR = 0.72; 95% CI, 0.29–1.49), or for leukemia (SIR = 0.97; 95% CI, 0.78–1.21). No effect was seen also by type of phone (analogue or digital), duration of use, or time or age since first subscription. The large study size meant the authors were able to assess many different types and subtypes of cancer with reasonable precision. Also, being population–based, this study avoided problems associated with incomplete ascertainment or participation of subjects. However, it was not able to adjust for other modifiers of risk, and the study investigators did not have information specifically on the phone user or use of corporate cellular phones.

In a population–based case–control study of 1617 cases of brain tumour identified and still alive in Sweden from January 1997 to June 2000 (Hardell et al., 2002a), a 30% increased risk was observed among users of analogue phones, which rose to 80% for those with greater than 10 years' use. The increase was confined to those with benign tumours, in particular acoustic neuromas. Laterality of phone use was also identified in this study as affecting risk for analogue phone users, for temporal and other areas of the brain. Users of cordless phones and digital cell phones showed no increased risk, but the follow–up time was shorter for these phone types. A separate analysis of 649 of the original 1111 cases of the malignant brain tumours only (Hardell et al., 2002b), showed no overall increased risk with cell phone use. Although use of either an analog or a digital phone on the same side of the head as the tumour for cases significantly increased risk of a brain cancer; a reduced risk was reported for those who used a phone on the opposite side of the head, which raises the possibility of reporting bias.

Data on acoustic neuroma, and benign and malignant brain tumours from the previous studies (Hardell et al., 2002a,b) were reported recently (Hardell et al., 2003a,b) with different analysis. The results show a non-statistically significant increased incidence of acoustic neuroma in the Swedish cancer registry between 1980–1998.

In Finland, a file of over 500,000 private cellular phone subscribers was linked to the cancer registry (Auvinen et al., 2002), and a case–control study of 398 brain tumour patients and 34 salivary gland tumour patients was carried out, using five controls per case. Information on type of phone (analog or digital), and start and end date of phone subscription was available. The analysis was adjusted for socioeconomic status, categories of urban status, and occupational groupings. Approximately 13% of the cases of brain tumours, 12% of the cases with salivary gland tumours, and 11% of the controls never had a personal subscription to a cellular phone provider. Average duration of subscription was 2–3 years for analog phone users, and less than 1 year for digital phone users. The OR for brain tumours with more than two years' phone use was 1.5 (95% CI, 0.9–2.5), based on only 18 cases; the OR for salivary gland tumours with more than two years' phone use was 2.3 (95% CI, 0.2–25.3), based on only 1 case. Two studies also reported on risk of acoustic neuroma with cellular phone use. Inskip found a non–significant increased risk of 1.4 (95% CI, 0.6–3.5) in his large case–control study (Inskip et al., 2001), whereas Muscat et al. (2002) reported the results of a hospital–based case–control study of acoustic neuroma cases, diagnosed from 1997 to 1999 in New York. They observed an adjusted OR of 0.7 (95% CI, 0.2–2.6) for greater than 60 total hours of use of a cellular phone, based on 9 cases. Risk did not vary significantly by frequency and duration of use.

Warren et al. (2003) explored the hypothesis that cellular phone use may cause intratemporal facial nerve (IFN) tumours. 18 patients with IFN tumour, diagnosed between 1995 and 2000, were matched with controls. Interviews were conducted and covered details of cellular phone use, medical history, occupational history, and personal habits. The surveys were completed by 18 subjects, and by controls with rhinosinusitis (72), or dysphonia or gastroesophageal reflux disease (69). 51 subjects with acoustic neuroma also completed the survey, and served as an alternative tumour group. There was no association with regular use of hand–held cellular phones in those with IFN tumour (OR = 0.4, 95% CI, 0.1–2.1) or in subjects with acoustic neuroma (OR = 1.0, 95% CI, 0.4–2.2). The OR of developing an IFN tumour with any hand–held cellular phone use was 0.6 (95% CI, 0.2–1.9). The authors caution that the number of subjects was small, and that the period of exposure was short.

Stang et al., (2001) reported on risk of uveal melanoma (melanoma of the eye) with self–reported occupational use of radio sets, mobile phones, or similar devices in a combined analysis of two case–control studies in Germany. A significant four–fold increase in risk was identified, based on 12 exposed cases. The authors speculate that RF radiation might act as a cancer promoter, by inhibiting melatonin production by cells in the retina and ciliary body, which in turn, might remove a block to proliferation of potentially cancerous cells. Exposure assessment in this study was insufficient for adequate characterization of exposure. In contrast, no relationship between cellular phone use and uveal melanoma was observed in the Danish cohort study (Johansen et al., 2001), based on eight cases of ocular cancer (SIR = 0.59; 95% CI = 0.25–1.17).

Other Radiofrequency Field Exposures

Cooper et al. (2001) updated the earlier studies by Dolk et al. (1997a,b) of adult and childhood leukemia around the Sutton Mast radio and TV transmitters in the West Midlands area of Great Britain. Cancer data from 1987 to 1994 indicated that none of the adult cancers had elevated risk within 2 km of the source, although over the entire study area within 10 km of the source, slight increase in risk of female hematopoietic and lymphatic cancers, specifically acute myeloid, all leukemias, and chronic lymphatic leukemia was seen; an increase was also seen in risk of male acute lymphatic leukemia. The original results of the Dolk study, a decreasing risk with distance for adult leukemia and some subgroups, were not replicated. There were too few childhood leukemia cases (26 in total) to reach conclusions on childhood leukemia risk.

Michelozzi et al. (2002) investigated the risk of adult and childhood leukemias near the Vatican high–power radio station in Rome, Italy. Forty adult leukemia deaths were reported between 1987 and 1998, within a 10–km radius of the station. The population of this area was 49,656 residents in 1991. Eight childhood leukemia cases were identified in the same area between 1987 and 1999. Although some variation in risk was observed for childhood leukemia with distance up to 6 km from the station (SIR = 2.2, 95% CI= 1.0–4.1), and there was the suggestion of a decrease in risk with increasing distance for childhood leukemia (p = 0.036) and for male adult leukemia mortality (p = 0.03), small numbers and the lack of individual exposure estimates preclude conclusions based on these results.

Occupational Exposed Populations

Results of a case–control study of neuroblastoma and parental occupational exposures to EM fields, specifically exposures to electrical equipment and radiation sources, were reported by De Roos et al. (2001). This study updates an earlier analysis based on parental job title (Olshan et al., 1999) of 538 cases from US and Canada and controls obtained through random digit dialling. This new analysis uses a job exposure matrix combining self–reported job title and exposures by source, reviewed by occupational hygienists, and grouped according to the major EM frequency range emitted by the source. Exposures to each source were evaluated separately. A slightly increased risk of neuroblastoma was seen among offspring of mothers who worked with RF–emitting equipment (OR = 2.8, 95% CI = 0.9–8.7), based on 12 cases, and using exposure data reviewed by industrial hygienists. ORs above 2 were reported for paternal exposures to mobile radio transmitters or stationary radar use, although overall, fathers' use of equipment emitting power–frequency, RF, or ionizing radiation resulted in ORs much closer to 1 (range 1.2–1.3). Use of cellular phones by mothers was not informative due to the small numbers involved (5 cases); for fathers' use, the OR was 1.1 based on 17 cases, using industrial hygienist assessment of exposure.

Groves et al. (2002) updated an earlier study (Robinette et al., 1980) on mortality related to microwave exposure in a cohort of 20,021 Korean War US navy technicians, as compared to other veterans deemed to be in low–exposure jobs. The original study did not find any adverse outcomes related to radar (RF) exposure, and this longer 40–year follow–up found an overall lower standardized mortality ratio, and lower risk of death from brain cancer or testicular cancer among the high–exposure occupations as compared to the low–exposure occupations. Mortality from leukemia was slightly, but not significantly, increased in the high–exposed group, and this increase was restricted to nonlymphocytic leukemia in only one of the three high–exposed occupations, that of electronic technicians in aviation squadrons. This large study with long follow–up is not supportive of the hypothesis that microwave exposures result in increased mortality, although the validity of the study results is weakened by the use of job title as a surrogate for exposure.

Epidemiologic Reviews

Elwood (2003) reviewed epidemiological studies of RF fields and cancer. He concludes: "The epidemiological results fall short of the strength and consistency of evidence that is required to come to a conclusion that RF emissions are a cause of human cancer. Although the epidemiological evidence in total suggests no increased risk of cancer, the results cannot be unequivocally interpreted in terms of cause and effect. The results are inconsistent, and most studies are limited by lack of detail on actual exposures, short follow–up periods, and the limited ability to deal with other relevant factors. In some studies, there may be substantial biases in the data used."

NEUROLOGICAL AND BEHAVIOURAL EFFECTS

A number of studies in both humans and animals have examined the possible effects of RF fields on neurological symptoms, cognitive function, electrical brain activity, and neurochemistry. The literature describing these effects is discussed below.

Human Studies

Neurological symptoms. Sandstrom et al. (2001) conducted an epidemiological study to test if

GSM phones users experience more symptoms than NMT users. In Sweden 6379 GSM users and 5613 NMT900 users were enrolled, and 2500 from each category in Norway. The adjusted OR did not indicate any increased risk for headache, warmth around/behind the ear, or discomfort, for GSM users compared with NMT users. However, a statistically significant association between calling time/number of calls per day and the prevalence headache, discomfort, and warmth was reported.

Koivisto et al. (2001) conducted a study on forty-eight human volunteers. They found that a 30–60 minute exposure to RF fields from GSM phones (902 MHz with 217 pulse modulation) had no detectable subjective effects such as headache, dizziness, fatigue, itching or tingling of the skin, and sensations of warmth on the skin.

Navarro et al. (2003) carried out a health survey in Murcia, Spain, in the vicinity of a cellular phone base station working in DCS-1800 MHz. The survey contained items related to "microwave sickness" or "RF syndrome." The microwave power density was measured at the respondents' homes. Statistical analysis showed a significant correlation between the declared severity of symptoms and measured power density.

Santini et al. (2003) administered questionnaires to 530 people (270 men, 260 women) living or not in proximity to BTSs. Eighteen different non-specific health symptoms (NSHS), described as RF sickness were examined. Certain complaints were reported only in the immediate vicinity of BTSs (up to 10 m for nausea, loss of appetite, and visual disturbances), whereas others were reported at greater distances from BTSs (up to 100 m for irritability, depressive tendencies, and lowering of libido, and up to 200 m for headaches, sleep disturbances, and feeling of discomfort). Fatigue was experienced significantly more often in the 200 to 300 m zone, as compared to the reference zone 300 m or more from the BTSs.

Cognitive function. Edelstyn and Oldershaw (2002) exposed thirty–eight volunteers who were assigned to two groups, an experimental that was exposed to a connected mobile phone, and a control group in which the phone was turned off. The experimental group was exposed to 900 MHz from a mobile phone for 30 minutes. Cognitive performance was assessed prior to mobile phone exposure, at 15 and 30 minutes post exposure. Significant differences between the two groups were evident after 5 minutes on two tests of attention capacity and one of processing speed. The authors concluded that in all three instances, performance was facilitated following mobile phone exposure.

Lee et al. (2003) randomly assigned 78 volunteers to an experimental or a control group. A GSM phone was mounted to the subject's head during the procedure with the earphone over the right ear. The participants did not know whether the phone was on or off. Two tasks of attention were performed while the phone was on in the experimental group and off in the control group. The subjects were required to complete the tasks within 25 minutes, and after a 2–minute rest the tasks were repeated, but the phone was switched off in both groups. There was no difference between the groups in the reaction times or in the number of correct responses in the first task. Reaction time in both groups significantly improved in the second trial, suggesting a practice effect. In this task, the experimental group improved its reaction time in the second trial significantly more than the controls. The authors suggest that attention functions may be differentially enhanced after exposure to the EM field emitted by mobile phones. Furthermore, this transient facilitation effect might be dose dependent. In the second task, there was no significant difference in performance between the two groups, although both the experimental and the control group improved in the second trial.

Haarala, et al. (2003) conducted a study to replicate results obtained in a previous study (Koivisto et al., 2000) on effects of the EM fields emitted by a 902 MHz mobile phone on human cognitive functioning, but with methodological improvements. The results of their study indicated that EM fields had no effect on reaction times or on the accuracy of the subjects' answers. They conclude that EM fields had no immediate effect on human cognitive functioning or that such effects are so small that they are observed on behaviour only occasionally.

Smythe and Costall (2003) randomly assigned 62 healthy volunteers (33 men, 29 women) to one of three experimental conditions: no phone exposure; exposure to 1800 MHz mobile phone (SAR 0.79 W/kg); and inactive phone exposure. They were provided with a series of words to learn, structured in a two–dimensional shape, and given 3 minutes to memorize the words. After a 12–minute distraction task they were then asked to draw the shape (spatial) and place the correct words (semantic) into the appropriate boxes. The results showed that the males exposed to an active phone made fewer spatial errors than those exposed to an inactive phone. The subjects, however, were randomised without reference to gender, and the gender analysis appears to have been post hoc. When the "no phone" group was included in the analysis there was no significant difference in the number of errors. Furthermore, the results were inconsistent. Males had more errors in the spatial recall task, although the results were not statistically significant.

A recent study from the Netherlands has examined the effects of RF signals from mobile phone base stations on feelings of well being and cognitive functions. Zwamborn et al. (2003) recruited 36 subjects who had reported complaints that they attributed to GSM exposure from base station antennas. Another 36 subjects without these complaints also participated. Feelings of well being were assessed by a questionnaire after actual or sham exposure, and cognitive functions were measured during RF exposure. They were exposed to SARs between 0.064 and 0.078 mW/kg at 900 MHz and 1800 MHz by replicating GSM fields, and also the 2100 MHz UMTS (3G) fields. The study found a statistically significant relation between the UMTS fields and feelings of well being for both the sensitive and the control group. No such effect was seen for the GSM at 900 and 1800 MHz. Some effects were observed also in cognitive function tests but there were a higher number in the control group than the sensitive group, and the pattern of these results is quite variable.

The examination of the effect of EM exposure emitted by mobile phones on human attention revealed that mobile phone users performed better on one of the three measures of attention than did the non–mobile phone users. Hocking and Westerman (2001) reported a neurological abnormality in a patient after accidental exposure of the left side of the face to a CDMA mobile phone radiation from a down–powered mobile phone base station antenna. The patient had headaches, unilateral left blurred vision and pupil constriction, unilateral altered sensation on the forehead, and abnormalities of current perception thresholds on testing the left trigeminal ophthalmic nerve. The authors suggested that exposure to EM fields emitted by mobile phones may have a mild facilitating effect on the attention functions. They concluded that the result of their study is consistent with previous observations that such exposure has a facilitating effect on cognitive processing.

Electrical activity. In an investigational analysis, Lebedeva et al. (2001) found that, when human beings were exposed to EM field of mobile phones, their cerebral cortex biopotentials revealed an increase in the alpha range power density as compared to the placebo experiment. The dimension of electroencephalogram (EEG) correlation dynamics and the relation of sleep stages changed under the influence of mobile phone exposure.

Croft et al. (2002) measured both resting EEG and phase–locked neural responses to auditory stimuli of 24 human subjects while a mobile phone was either operating, or turned off. Mobile phone exposure altered resting EEG, decreasing 1–4 Hz activity (right hemisphere sites), and increasing

8–12 Hz activity as a function of exposure duration (midline posterior sites). Mobile phone exposure also altered early phase–locked neural response, attenuating the normal response decrement over time in the 4–8 Hz band, decreasing the response in the 12-30 Hz band globally and as a function of time, and increasing midline frontal and lateral posterior responses in the 30–45 Hz band. Authors concluded that active mobile phones affect neural function in humans and do so as a function of exposure duration.

Huber et al. (2002) investigated the effect of RF fields versus sham control exposure on waking regional cerebral blood flow, and on waking and sleep EEG in humans in two experiments. In the first experiment, positron emission tomography scans were taken after unilateral head exposure to 30 minutes pulsed modulated 900 MHz RF field. In the second experiment night time sleep was polysomnogarphically recorded after RF exposure. Pulse–modulated RF exposure increased regional cerebral blood flow in the dorsolateral prefrontal cortex ipsilateral to exposure. Also, night time RF exposure enhanced EEG power in the alpha frequency range prior to sleep onset, and in the spindle frequency range during the second phase of sleep. Exposure to RF fields without pulse modulation did not enhance power in the waking or sleep EEG. Huber et al. (2003) further reported an extended analysis to the previous study, as well as, the detailed dosimetry of the brain areas, including the assessment of the exposure variability and uncertainties. Compared EEG was initially increased in the 9–14 Hz range in both experiments. No topographical differences with respect to the effect of RF exposure were observed in the two experiments. Even unilateral exposure during waking induced a similar effect in both hemispheres.

Kramarenko and Tan (2003) used a 16-channel telemetric EEG to record changes during exposure of human skull to EM fields emitted by a mobile phone. Spatial distribution of EM fields was especially concentrated around the ipsilateral eye adjacent to the basal surface of the brain. Traditional EEG was full of noises during operation of a cellular phone. Using a telemetric EEG in awake subjects, all the noise was eliminated, and EEG showed interesting changes: after a period of 10-15 s there was no visible change, the spectrum median frequency increased in areas close to antenna; after 20-40 s, a slow-wave activity (2.5-6.0 Hz) appeared in the contralateral frontal and temporal areas. These slow waves lasting for about one second repeated every 15-20 s at the same recording electrodes. After turning off the mobile phone, slow-wave activity progressively disappeared; local changes such as increased median frequency decreased and disappeared after 15-20 min. Similar changes were observed in children, but the slow-waves with higher amplitude appeared earlier in children (10-20 s) than adults, and their frequency was lower (1.0-2.5 Hz) with longer duration and shorter intervals. The results suggested that cellular phones may reversibly influence the human brain, inducing abnormal slow waves in EEG of awake persons.

Hocking and Westerman (2003) conducted a literature search for case reports and case series regarding peripheral neurological effects of RF radiation, mainly noxious sensations or dysaesthesia. The collected data revealed that cases have arisen after exposure to much of the RF range. In some cases, symptoms are transitory but lasting in others. After very high exposure, nerves may be grossly injured. After lower exposure, which may result in dysaesthesia, ordinary nerve conduction studies find no abnormality but current perception threshold studies have found abnormalities. Only a small proportion of similarly exposed people develop symptoms.

Summary of results. Some studies suggest that some aspects of cognitive functions and measures of brain physiology may be affected while others do not. These include changes in memory tasks, response patterns, normal sleeping EEG patterns, and other brain functional changes although a Few studies have demonstrated improved cognitive functions in volunteers exposed to RF radiation in the frequency range of mobile phones. Subjective symptoms such as dizziness, disorientation, nausea, headache, and other unpleasant feelings might be a direct result of RF fields although such symptoms are very general and may have many other causes. Wilén et al. (2003) made use of the information about prevalence of symptoms, calling time per day, and number of calls per day from a previous epidemiological study (Sandstrom et al., 2001). They combined it with measurements of the SAR of the specific mobile phone used by each person included in the above study. Two new exposure parameters (have been) were devised: specific absorption per day (SAD) and specific absorption per call (SAC). The results indicated that SAR values > 0.5 W/kg may be an important factor for the prevalence of some of the subjective symptoms, especially in combination with long calling times per day.

Animal Studies

Cognitive function. Dubreuil et al. (2002) studied the performance of rats using a head–only exposure system emitting a 900 MHz GSM EM field (pulsed at 217 Hz) for 45 minutes (SAR = 1 and

3.5 W/kg). Two behavioural tasks have been used to demonstrate performance deficits in spatial learning after EM field exposure: a classical radial maze elimination task and a spatial navigation task in an open–field arena (dry–land version of the Morris water maze). The performances of rats exposed for 45 minutes to 900–MHz (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. In another study aimed at extending these results with more complex spatial learning tasks and a non-spatial task, Dubreuil et al. (2003) reported that mobile phone RF radiation (45 minutes head-only exposure to 900 MHz GSM at densities between 1 and 3.5 W/kg) had no effect on spatial and non-spatial memory of rats.

Yamaguchi et al. (2003) suggest that the exposure to a pulsed 1439 MHz TDMA field at levels about four times stronger than emitted by mobile phones (SAR of 7.5 W/kg or 25 W/kg for either 1 hour daily for 4 days or for 4 weeks) does not affect the learning and memory processes in rats when there are no thermal effects.

Electrical activity. Marino et al. (2003b) studied the effect of EM field from a cellular telephone on brain electrical activity, using a novel analytical method based on a nonlinear model. The EEG from rabbits was embedded in phase space and local recurrence plots were calculated and quantified using recurrence quantitation analysis. When the rabbits were exposed to the radiation (800 MHz band, 600 mW) under conditions that simulated normal human use, the EEG was significantly affected in nine of ten animals studied. The effect occurred beginning about 100 ms after initiation of application of the field and lasted approximately 300 ms. In each case, the fields increased the randomness in the EEG. A control procedure ruled out the possibility that the observations were a product of the method of analysis. No differences were found between exposed and control epochs in any animal when the experiment was repeated after the rabbits had been sacrificed, indicating that absorption of radiation by the EEG electrodes could not account for the observed effect. No effect was seen when deposition of energy in the brain was minimized by repositioning the radiating antenna from the head to the chest, showing that the type of tissue that absorbed the energy determined the observed changes in the EEG. The authors concluded that, in normal use, the fields from a standard cellular telephone can alter brain function as a consequence of absorption of energy by the brain.

Neruochemical effects. Testylier et al. (2002) observed the neurochemical modification of the hippocampal cholinergic system during and after exposure to low intensity RF fields. The acetylcholine release in the brain of freely moving rats exposed for 1 hour during the day to a 2.45–GHz CW RF field (2 or 4 mW/cm^2) was measured. Rats exposed at 2 mW/cm^2 did not show significant modification in acetylcholine release, whereas those exposed at 4 mW/cm^2 showed a significant 40% decrease in mean acetylcholine release from hippocampus.

Neurological Reviews

During the past few years, there have been inconsistencies in results between experiments due to various experimental protocols and EM exposure characteristics. Major reviews have evaluated the literature on neurological and behavioural effects and concluded their findings. For example, Cook et al. (2002) reported that: "Experimental investigations of weak EM field (including RF fields–ELF associated with mobile phones) effects on human physiology have yielded some evidence of an effect in a number of different areas, such as heart rate variability, sleep disturbance and melatonin suppression."

Hamblin and Wood (2002) reviewed 14 published papers of the effects of mobile phone RF fields on human brain activity and sleep. They concluded that while the studies are inconsistent and comparison between individual studies is difficult, there is some evidence for effects on EEG. They further reported that "current international safety standards do appear to be adequate to minimize the possibility of harm, if the currently reported effects become substantiated."

In another review of the studies of effects of mobile phones on brain function and behaviour, Hossmann and Hermann (2003) concluded: "Most of the reported effects are small as long as the radiation intensity remains in the nonthermal range. However, health risks may evolve from indirect consequences of mobile telephony, such as the sharply increased incidence rate of traffic accidents caused by telephony during driving, and possibly also by stress reactions which annoyed bystanders may experience when mobile phones are used in public places."

Recently, D'Andrea et al. (2003b) reviewed the recent literature concerning RF exposure and behavioural and cognitive effects. They conclude: "Reports of change of cognitive function (memory and learning) in humans and laboratory animals are in the scientific literature. Mostly, these are thermally mediated effects, but other low level effects are not so easily explained by thermal mechanisms. The phenomenon of behavioural disruption by microwave exposure, an operationally defined rate decrease (or rate increase), has served as the basis for human exposure guidelines since the early 1980s and still appears to be a very sensitive RF bioeffect. Nearly all evidence relates this phenomenon to the generation of heat in the tissues and reinforces the conclusion that behavioural changes observed in RF exposed animals are thermally mediated. Such behavioural alteration has been demonstrated in a variety of animal species and under several different conditions of RF exposure. Thermally based effects can clearly be hazardous to the organism and continue to be the best predictor of hazard for homosapiens. Nevertheless, similar research with man has not been conducted. Although some studies on human perception of RF exist, these should be expanded to include a variety of RF parameters."

AUTHORITATIVE REVIEWS

A number of authorities have conducted detailed reviews of the potential health risks associated with exposure to RF fields. The conclusions drawn from each of these reviews are summarized below.

American Cancer Society (2001)

The American Cancer Society conducted a review of the research on mobile phone technology and cancer and presented the findings in March, 2001. The review concludes: "There is now considerable epidemiological evidence that shows no consistent association between cellular phone use and brain cancer. The lack of ionizing radiation and the low energy level emitted from cell phones and absorbed by human tissues makes it unlikely that these devices cause cancer."

British Medical Association (2001)

The British Medical Association published a report on mobile phones and health that both summarizes available knowledge about mobile phones and health, and outlines on–going and planned research in this area. The report concludes: "The most recently published reviews of the literature have concluded that whilst there are small physiological effects within the existing guidelines, there are no definite adverse health effects from mobile phones or their base stations. However, all the main professional organizations have called for more research to be conducted, since the possibility that RF radiation may cause adverse effects cannot be ruled out on the currently available data. Clearly, there are large gaps in the knowledge that need to be addressed."

Director General of Health of France (Zmirou, 2001)

An expert group led by Dr. Denis Zmirou prepared a report to the Director General of Health of France concerning state of knowledge and recommendations about mobile phones, base stations and health. The report concluded: "Scientific data indicates, with comparative certainty, that due to RF exposure from a mobile phone, a variety of biological effects occur (e.g., EEG profile, reaction time, etc.) at energy levels that do not cause any local increase in temperature. However, in the current state of knowledge of these nonthermal effects, it is not yet possible to determine whether they represent a health hazard." The expert group recommended a risk management approach based on the precautionary principle, aimed at reducing public exposure to RF associated with mobile telephony to the lowest possible level compatible with service quality and justified by current scientific data.

European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Enviornment (CSTEE, 2001)

The European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) was requested to prepare an update of the opinion of the Scientific Steering Committee (SSC) on health effects of EM fields dated 1998 which endorsed the guidelines published by the ICNIRP. The CSTEE appointed a Working Group (WG) to evaluate the scientific findings resulting from new investigations. The WG concluded in its report: "The additional information which has become available on carcinogenic and other non–thermal effects of RF and microwave radiation frequencies in the last years does not justify a revision of exposure limits set by the Commission on the basis of the conclusions of the 1998 opinion of the SCC. In particular, in humans, no evidence of carcinogenicity in either children or adults has resulted from epidemiological studies."

Health Council of the Netherlands (2002)

The Health Council of the Netherlands prepared a report on the potential risks of EM fields from mobile telephones. The report concluded: "The EM field of a mobile telephone does not constitute a health hazard, according to the present state of scientific knowledge." However, the Council recommends conducting more research in the Netherlands on the influence of EM fields on cognitive functions. In a significant departure from the conclusions of the Independent Expert Group on Mobile Phones report (IEGMP, 2000), the Council does not recommend the application of the precautionary principle concerning nonthermal effects and finds no justification to recommend restriction in the use of mobile phones by children.

Institute of Electrical Engineers (IEE) Position Statement (IEE, 2002)

Every two years the IEE publishes on the worldwide web its Position Statement on the biological and health effects of low level EM fields and radiation principally attributable to power lines, mobile phones and base stations. In 2002, the IEE Policy Advisory Group on the Biological Effects of Low Level Electromagnetic Fields has concluded that there is still no convincing scientific evidence that shows harmful effects of low–level EM fields on humans. This conclusion is the same as that reached in its previous position statement, the last being in May 2000 and has not been changed by the peer reviewed literature of the past two years.

Swedish Radiation Protection Authority (Boice and McLaughlin, 2002)

The Swedish Radiation Protection Authority conducted a review of all published epidemiology studies of cellular phone use and cancer since 1996. The authors concluded that “in our view, a consistent picture has emerged from these studies that appear to rule out, with a reasonable degree of certainty, a causal association between cellular telephones and cancer to date. While the current state of the science is reassuring, ongoing case–control studies being conducted in 13 countries using a shared protocol, and continued follow–up of cohorts of cellular phone users, should provide further evidence regarding any possible carcinogenic effect associated with long–term cellular telephone use.”

World Health Organization (2002)

In response to public concerns, the World Health Organization (WHO) established the International Electromagnetic Fields (EMF) Project to assess the scientific evidence of possible health effects of EM fields. Specific studies have been identified to address the problem of localised exposure. The project has established a formal mechanism for reviewing the research results and conducting risk assessments of EM exposure. It is also developing public information materials, and bringing together standards groups worldwide in an attempt to harmonise international exposure standards.

WHO is also conducting a large–scale epidemiology study being coordinated in over 13 countries through the International Agency for Research on Cancer (IARC), an agency of WHO, to identify if there are links between use of mobile phones and head and neck cancers. Further details of the study are described by Cardis and Kilkenny (1999). Field work for the study is expected to be completed by the end of 2003 (WHO, 2000), with final results to be reported following a careful assessment of the data from this important international investigation.

Australian Government (2003)

The Australian government conducted an inquiry into the safety of mobile phone technology. The inquiry found no substantiated scientific evidence of health effects from mobile phones and their base stations. The inquiry reiterated that mobile phones must comply with strict safety guidelines established by the government.

CONCLUSIONS

The widespread use of devices that emit RF fields, notably wireless telecommunication devices such as mobile phones, has resulted in increased potential for RF field exposure. The potential health risks from RF fields were reviewed in detail by the Royal Society of Canada (1999). At that time, the panel conducting this review concluded that existing RF guidelines were largely protective of human health based on the scientific evidence available at that time, but noted several RF fields appeared to be associated with certain biological effects of no known clinical significance that required clarification. The panel also made a number of research recommendations, the most important of which was the conduct of a large–scale epidemiologic study of the potential cancer risks from mobile phone use. The results of the ongoing WHO study of mobile phones will provide important new information in this regard (cf. WHO, 2000).

Subsequently, the IEGMP (2000) re–affirmed the conclusions reached by the Royal Society of Canada (1999). All of the authoritative reviews completed within the last two years have concluded that there is no clear evidence of adverse health effects associated with RF fields from mobile phones.

The British Medical Association (2001), for example, concluded that “whilst there are small physiological effects within the existing guidelines, there are no definite adverse health effects from mobile phones or their base stations”. At the same time, these same reviews support the need for further research to clarify the possible associations between RF fields and adverse health outcomes that have appeared in some reports, including possible associations with brain cancer (Hardell et al., 2002a,b, 2003a,b). Research on the biological effects of low–level RF fields (including modulated signals), such as alteration of enzyme activity and transport of ions across cellular membranes, is also encouraged. Given the advances in human functional and molecular brain imaging and mapping methods (Huber et al., 2002), research using these techniques may help to elucidate the functional and anatomical correlates of such biological effects.

The potential health risks of RF fields should be continually reassessed as new research results become available. RF exposure guidelines also need to be updated as new scientific information on RF fields and health risks is generated. The authors of the present update of the original Royal Society of Canada review will continue to monitor the scientific literature on RF fields and health, and plan to provide future updates as new scientific information is reported in the literature.

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