Bioelectromagnetics 32:511–534 (2011)

Review

Review of Possible Modulation-Dependent Biological Effects of Radiofrequency Fields

Jukka Juutilainen,* Anne Höytö, Timo Kumlin, and Jonne Naarala

Department of Environmental Science, University of Eastern Finland, Kuopio, Finland

The biological effects of modulated radiofrequency (RF) electromagnetic fields have been a subject of debate since early publications more than 30 years ago, suggesting that relatively weak amplitude-modulated RF electromagnetic fields have specific biological effects different from the well-known thermal effects of RF energy. This discussion has been recently activated by the increasing human exposure to RF fields from wireless communication systems. Modulation is used in all wireless communication systems to enable the signal to carry information. A previous review in 1998 indicated that experimental evidence for modulation-specific effects of RF energy is weak. This article reviews recent studies (published after 1998) on the biological effects of modulated RF fields. The focus is on studies that have compared the effects of modulated and unmodulated (continuous wave) RF fields, or compared the effects of different kinds of modulations; studies that used only one type of signal are not included. While the majority of recent studies have reported no modulation-specific effects, there are a few interesting exceptions indicating that there may be specific effects from amplitude-modulated RF fields on the human central nervous system. These findings warrant follow-up studies. Bioelectromagnetics 32:511–534, 2011.

Key words: electromagnetic fields; mobile phones; health effects; non-thermal effects

INTRODUCTION

The biological effects of modulated radiofrequency (RF) electromagnetic fields have been a subject of debate since early publications suggesting that relatively weak amplitude-modulated RF electromagnetic fields have specific biological effects different from the well-known thermal effects of strong RF fields [Bawin et al., 1975; Blackman et al., 1980]. This discussion has been recently activated by the increasing human exposure to RF energy from wireless communication systems. Modulation is used in all wireless communication systems to enable the signal to carry information. The question of possible modulation-specific effects is of fundamental importance for the direction of future research on biological and health effects of RF electromagnetic fields. New RF technologies are introduced frequently, and there are views that all new technologies (new modulation characteristics) should be tested analogously to toxicological testing of new chemicals. Obviously, this approach would require a lot of resources. An alternative, more science-based approach would be to try to understand the mechanisms of any modulation-specific effects and to identify modulation characteristics that are responsible for such effects. In any case, the first step is to establish whether any modulation-specific effects exist. Previous reviews have indicated that experimental evidence for modulation-specific effects of RF energy is weak and that no plausible biophysical mechanisms have been established for such responses at environmental field levels [Juutilainen and de Seze, 1998; NCRP, 2003; Foster and Repacholi, 2004]. This article reviews recent studies (published after the 1998 review by Juutilainen and de Seze) on the biological effects of modulated RF fields. The articles included in this review were identified through the recent comprehensive review by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) [2009] and by a literature search using PubMed. The literature search attempted to cover all studies on the bioeffects of RF fields published since 1998; the articles relevant to possible modulation-specific effects were identified by reading the abstracts. Inclusion in the review required that the study had

*Correspondence to: Jukka Juutilainen, Department of Environmental Science, University of Eastern Finland, Kuopio, Finland
E-mail: jukka.juutilainen@uef.fi

Received for review 7 September 2010; Accepted 4 January 2011

DOI 10.1002/bem.20652
Published online 7 April 2011 in Wiley Online Library (wileyonlinelibrary.com).

compared the effects of modulated and unmodulated (continuous wave, CW) RF fields, or compared the effects of different kinds of modulations. While almost all recent studies on bioeffects of RF fields have used modulated signals (similar to those emitted by mobile communication systems), most of them have not compared experimental groups that differ with respect to existence or type of modulation. Without such a comparison, it is impossible to conclude whether the effects (or lack of effects) observed are related to the modulation used or to RF energy per se. The scope of the review was limited to modulations used in telecommunications. The well-established auditory responses [Elder and Chou, 2003] and other biological effects from pulsed microwaves with high peak power [e.g., Pakhomov et al., 2000, 2002, 2003] were not reviewed.

MODULATION OF RF ELECTROMAGNETIC FIELDS

An unmodulated RF electromagnetic field consists of sinusoidal oscillations at a single frequency between 0.1 MHz and 300 GHz. Modulation is used to make the signal carry information. A wide variety of modulation methods are used in different telecommunication technologies. Most of these involve variations in the amplitude or frequency of the signal. In amplitude modulation (AM), the carrier wave is modulated by a low frequency signal (Fig. 1). Similarly, frequency modulation (FM) involves modulation of the frequency so that it varies in a narrow band around the basic frequency, and phase modulation involves changes in the phase of the signal. A form of amplitude modulation is pulse modulation (PM), such as that used in radars, which emit very high-intensity, short-duration pulses. While rather basic AM and FM signals have been used in radio broadcasting and in analogue mobile phones, modern digital telecommunication technologies are based on complex modulation schemes that include combinations of different forms of modulation. A Global System for Mobile Communications (GSM) mobile phone, for example, emits 577 ms pulses that are repeated at a rate of 217 Hz, and the digital information is transmitted during the pulses using a type of FM. The pulsing at 217 Hz results from the Time Division Multiple Access (TDMA) channel access method used in GSM. In mobile communication systems, the same radio channel is shared between several users using different channel access methods. In TDMA, access is divided by time; transmission from each user occurs within a short time slot (577 ms in GSM), which results in pulsed transmission. In contrast, Frequency Division Multiple Access (FDMA) divides access by frequency. The 3rd generation Universal Mobile Telecommunications System (UMTS) phones use Code Division Multiple Access (CDMA), which employs user-specific codes to divide access between users. A CDMA signal is not regularly pulsed and is more continuous than a TDMA signal, but the adaptive power control of UMTS checks and adjusts the output power 1500 times per second, which results in some amplitude variations at 1500 Hz. Characteristics of some common digital communication systems are compared in Table 1. Only simplified descriptions of the signals are given in Table 1; the true mobile communication signals are complex and include other modulations in addition to the basic pulse frequencies. It should also be noted that the modulation characteristics of mobile phone handsets are different from those of base stations. In GSM, for example, each handset communicates with the base station using the pulsed signal described above. However, the base station communicates with many handsets, one after the other, which results in much more continuous signal. The ongoing changes in mobile communication technology (such as replacement of GSM by UMTS) favour modulations that include less amplitude variations than the current and most common GSM signals.

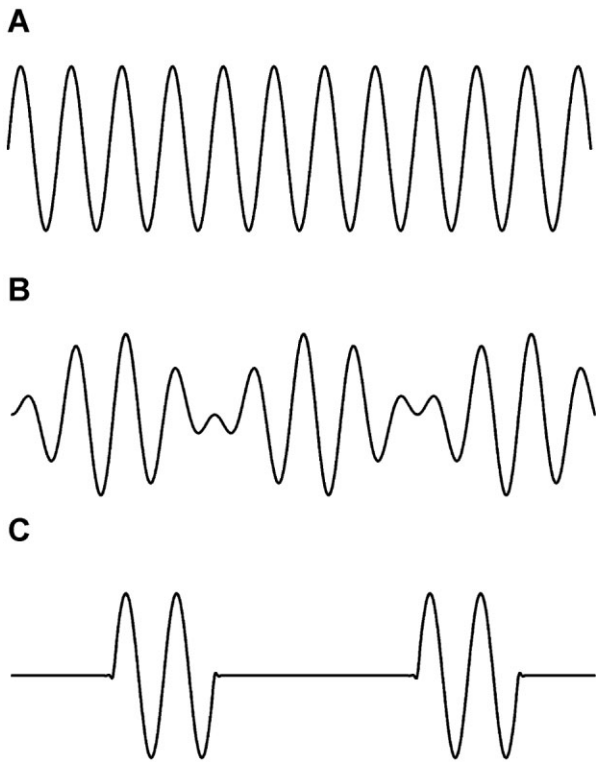

Fig. 1. Schematic representation of an unmodulated (continuous) wave (**A**) and two forms of amplitude modulation: waves modulated with a smoothly varying (**B**) or pulsed (**C**) signal.

TABLE 1. Characteristics of Some Mobile Communication Systems

Mobile communication system	Frequency, MHz	Channel access method	Variations in amplitude
D-AMPS (Digital Advanced Mobile Phone System)	850	TDMA	Pulsed, 50 Hz
GSM (Global System for Mobile Communications)	900–1900	TDMA	Pulsed, 217 Hz
TETRA (Terrestrial Trunked Radio)	400	TDMA	Pulsed, 17 Hz
UMTS (Universal Mobile Telecommunications System)	2100	CDMA	Less than in TDMA, but some variation at 1500 Hz due to adaptive power control

CDMA, Code Division Multiple Access; TDMA, Time Division Multiple Access.

REVIEW OF EXPERIMENTAL OBSERVATIONS

Genotoxicity

Studies on genotoxicity are described in Table 2. DNA damage in cultured cell lines was evaluated by using single cell gel electrophoresis (Comet) assay in 11 studies. Various human cell lines (normal and diploid fibroblasts, lymphocytes, glioblastoma cells, neuroblastoma cells, glioblastoma cells and leucocytes) as well as rat granulosa cells and mouse fibroblasts were used. In most of the studies, no effects of RF field exposure were seen [Malyapa et al., 1997; Li et al., 2001; Maes et al., 2001; Tice et al., 2002; McNamee et al., 2003; Hook et al., 2004b; Sakuma et al., 2006; Luukkonen et al., 2010]. Both increased and decreased DNA damage was reported in human Molt-4 lymphoblastoid cells after very low-level RF field exposure [Phillips et al., 1998]. The effects depended on modulation and exposure level, so that increased damage was seen at the highest level of exposure to an Integrated Digital Enhanced Network (iDEN) signal, whereas exposure to a TDMA and the lowest iDEN level signals resulted in a 'protective effect'. Diem et al. [2005] reported induction of DNA single- and double-strand breaks in human diploid fibroblasts and transformed GFSH-R17 rat granulosa cells after exposure to 1800 MHz RF energy using continuous waves and two GSM-type signals with different modulation characteristics. The effects reported in this controversial [see Lerchl and Wilhelm, 2010] paper did not depend on modulation, however. Increased DNA damage in human neuroblastoma cells was recently reported after combined exposure to menadione (a chemical that induces intracellular production of reactive oxygen species, ROS) and CW exposure at 972 MHz [Luukkonen et al., 2009]. However, no effect was observed in cells exposed to a GSM-modulated signal. The finding is surprising, and there is no known or hypothetical mechanism for effects from a CW signal but not from a pulse-modulated signal at identical exposure levels.

Several in vitro studies of micronucleus induction in mouse embryo fibroblasts [Bisht et al., 2002], human leucocytes [Tice et al., 2002; McNamee et al., 2003; Zeni et al., 2003] and human lymphocytes [d'Ambrosio et al., 2002; Vijayalaxmi, 2006] have been published since 1998. Only one reported statistically significant effects; increased micronucleus frequency was found following exposure to a 1748 MHz phase-modulated RF field, but not after corresponding exposure to a CW field [d'Ambrosio et al., 2002]. Juutilainen et al. [2007] investigated the effects of long-term exposure to three different mobile phone signals in three strains of mice. Blood samples for micronucleus analysis were taken from the animals of two long-term co-carcinogenicity studies [Heikkinen et al., 2001, 2003]. No effects on micronucleus frequency were observed from any of the exposures used.

Three studies have investigated effects of pulsed and CW RF on chromosomal aberrations. No effects in mouse cells [Komatsubara et al., 2005] or in human lymphocytes [Maes et al., 2001; Vijayalaxmi, 2006] were seen.

Changes in the conformation of chromatin and formation of 53BP1/gammaH2AX DNA repair foci were reported in lymphocytes from hypersensitive and healthy subjects following exposure to 915 MHz GSM and 1947 MHz UMTS signals [Belyaev et al., 2009]. The effects did not depend on the type of the signal. No effects on sister chromatid exchange were found in human lymphocytes that were exposed to pulsed or GSM-modulated 380, 900 and 1800 MHz RF fields [Antonopoulos et al., 1997]. No effects on neoplastic transformation were observed in mouse C3H/10T1/2 fibroblasts exposed to FDMA or CDMA signals for 4 or 42 days [Roti Roti et al., 2001].

In Vitro Studies on Cancer-Relevant Non-Genotoxic Effects

Several biological endpoints related to growth, oxidative stress and cell death have been studied in cell cultures exposed to RF fields (Table 3). The majority of these studies have been negative.

Several studies have measured the activity of ornithine decarboxylase (ODC), an enzyme that reflects

TABLE 2. Studies on Genotoxicity

Experimental model	Exposure	Modulation	Findings	Evidence for modulation-specific effect?	Comment	Refs.
DNA strand breaks in mouse C3H/10T1/2 fibroblasts and human U87MG glioblastoma cells	836 or 848 MHz, 0.6 W/kg for 2, 4 or 24 h	CDMA (848 MHz) or FMCW (836 MHz)	No effects	No		Malyapa et al. [1997]
DNA strand breaks in human Molt-4 lymphoblastoid cells	814 MHz, 2.4 or 24 mW/kg or 836 MHz, 2.6 or 26 mW/kg, for 2, 3 or 21 h	iDEN (814 MHz) or TDMA (836 MHz)	'Protective' effect for TDMA and iDEN (lowest exposure) and increased damage at highest iDEN exposure	Yes		Phillips et al. [1998]
DNA strand breaks in mouse C3H/10T1/2 fibroblasts	836 MHz or 848 MHz, 3.2–5.1 W/kg for 2, 4 or 24 h	FDMA (836 MHz) or CDMA (848 MHz)	No effects	No		Li et al. [2001]
DNA strand breaks, chromosomal aberrations and SCEs in human lymphocytes	900 MHz, 0–10 W/kg for 2 h	GSM dummy burst, GSM pseudo random or CW	No effects	No	Combined exposures with MMC or X-rays	Maes et al. [2001]
DNA strand breaks and apoptosis in human Molt-4 lymphoblastoid cells	848 or 836 MHz, 3.2 W/kg; 814 MHz, 2.4–24 mW/kg; 837 MHz, 2.6–26 mW/kg, for 2, 3 or 21 h	CDMA (848 MHz), FDMA (836 MHz), iDEN (814 MHz) or TDMA (837 MHz)	No effects	No		Hook et al. [2004b]
DNA strand breaks in human diploid fibroblasts and rat GFSH-17 granulosa cells	1800 MHz, 1.2 or 2 W/kg for 4, 16 or 24 h (continuous or intermittent 5 min on, 10 min off)	GSM-Basic, GSM-Talk or CW	Induction of DNA single- and double-strand breaks after 16 and 24 h in both cell types and with different mobile phone modulations	No		Diem et al. [2005]
DNA strand breaks in human A-172 glioblastoma cells and human IMR-90 fibroblasts	2.14 GHz, 80–800 mW/kg for 2 or 24 h	W-CDMA or CW (only 80 mW/kg)	No effects	No		Sakuma et al. [2006]
DNA strand breaks and ROS production in human SH-SY5Y neuroblastoma cells	872 MHz, 5 W/kg for 1 h	GSM or CW	DNA breakage and ROS production were increased in cells co-exposed to menadione and CW RF	Yes	Combined exposure with menadione	Luukkonen et al. [2009]
DNA strand breaks and ROS production in human SH-SY5Y neuroblastoma cells	872 MHz, 5 W/kg for 1 or 3 h	GSM or CW	No effects	No	Combined exposure with $FeCl_2$ or $FeCl_2$ + DEM	Luukkonen et al. [2010]
DNA strand breaks and micronucleus induction in human leukocytes	1900 MHz, 0.1–10 W/kg for 24 h	Pulsed or CW	No effects	No		McNamee et al. [2003]
DNA strand breaks and micronucleus induction in human leukocytes	837 or 1910 MHz, 1–10 W/kg for 3 or 24 h	FM, CDMA or TDMA (837 MHz); GSM (1910 MHz)	Increase in micronuclei after 24 h exposure at 5 or 10 W/kg	No		Tice et al. [2002]

Micronucleus induction in mouse C3H/10T1/2 fibroblasts	836 MHz, 3.2 or 5.1 W/kg or 848 MHz, 3.2 or 4.8 W/kg for 3, 8, 16 or 24 h	FDMA (836 MHz) or CDMA (848 MHz)	No effects	No		Bisht et al. [2002]
Micronucleus induction in human lymphocytes	1748 MHz, 5 W/kg for 15 min	GMSK phase modulation or CW	Micronucleus frequency was affected by GMSK but not by CW exposure	Yes	No effects on proliferation kinetics	d'Ambrosio et al. [2002]
Micronucleus induction and proliferation in human white blood cells	900 MHz, 0.2 or 1.6 W/kg, intermittently 6 min on/3 h off for 44 h, 6 min on, 3 h off for 24 h or 1 h/day for 3 days	GSM or CW	No effects	No		Zeni et al. [2003]
Micronucleus induction in mouse erythrocytes	903 MHz, 1.5 W/kg or 902 MHz, 0.35 W/kg for 78 weeks; 902 or 849 MHz, 0.5 W/kg for 52 weeks; 1.5 h/day, 5 days/week	NMT (903 MHz), GSM (902 MHz) or DAMPS (849 MHz)	No effects	No		Juutilainen et al. [2007]
Chromosomal aberrations and micronucleus induction in human lymphocytes	2.45 GHz, 2.13 W/kg or 8.2 GHz, 20.7 W/kg for 2 h	Pulsed at 10 kHz (2.45 GHz) or 50 kHz (8.2 GHz)	No effects	No	PHA was used to stimulate cells	Vijayalaxmi [2006]
Chromosomal aberrations in mouse m5S cells	2450 MHz 5, 10, 20, 50 or 100 W/kg for 2 h	Pulsed or CW	No effects	No		Komatsubara et al. [2005]
SCE and cell cycle progression in human lymphocytes	380 MHz, 0.08 W/kg, 900 MHz, or 1800 MHz, 0.2 W/kg for 48–68 h	Pulsed at 17.65 Hz (380 MHz) or GSM	No effects	No		Antonopoulos et al. [1997]
Conformation of chromatin and 53BP1/γH2AX DNA repair foci in human lymphocytes from hypersensitive and healthy persons	905 or 915 MHz, 37 mW/kg; 1947 MHz, 40 mW/kg for 1 h	GSM (37 mW/kg) or UMTS (40 mW/kg)	Both endpoints were affected after exposure to 915 MHz GSM and 1947 MHz UMTS	No		Belyaev et al. [2009]

CW, continuous wave; DEM, diethyl maleate; DNA, deoxyribonucleic acid; FDMA, Frequency Division Multiple Access; FMCW, Frequency Modulated Continuous Wave; GMSK, Gaussian Minimum Shift Keying; iDEN, Integrated Digital Enhanced Network; MMC, mitomycin C; NMT, Nordic Mobile Telephony; PHA, phytohemaglutinin; PW, pulse wave; ROS, reactive oxygen species; SAR, specific absorption rate; SCE, sister chromatid exchange; W-CDMA, Wideband Code Division Multiple Access. For other abbreviations, see Table 1.

TABLE 3. In Vitro Studies: Cancer-Related Non-Genotoxic Endpoints

Experimental model	Exposure	Modulation	Findings	Evidence for modulation-specific effect?	Comment	Refs.
ODC activity in L929 mouse fibroblasts	900 MHz, 0.2 or 0.4 W/kg for 2, 8 or 24 h	GSM or CW	No effects	No		Höytö et al. [2006]
ODC activity in mouse L929 fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells and rat primary astrocytes	872 MHz, 1.5, 2.5 or 6 W/kg for 2, 8 or 24 h	GSM or CW	No effects in secondary cell lines, decreased ODC, activity in rat primary astrocytes	No		Höytö et al. [2007a]
ODC activity in mouse L929 fibroblasts	835 MHz, 2.5 or 6 W/kg for 2, 8 or 24 h; 872 MHz, 6 W/kg for 8 h	DAMPS or CW	Increased ODC activity at 872 MHz. No effects at 835 MHz except for decreased ODC activity related to heating of the cells	No	Different exposure systems at 835 and 872 MHz	Höytö et al. [2007b]
ODC activity, proliferation and apoptosis in L929 murine fibroblasts	872 MHz, 5 W/kg for 1 or 24 h	GSM or CW	No effects	No	Cells were stimulated with fresh medium or stressed with serum deprivation	Höytö et al. [2008b]
ODC activity in human SH-SY5Y neuroblastoma cells	1800 or 835 MHz, 1 or 2.5 W/kg for 8 or 24 h	GSM (1800 MHz) or DAMPS (835 MHz)	No effect	No		Billaudel et al. [2009a]
ODC activity in mouse L929 fibroblasts	900 MHz, 0.5, 1 or 2.5 W/kg for 8 h; 835 MHz, 0.5–6 W/kg for 7–8 h; 1800 MHz, 2.5 W/kg for 2, 8 or 24 h	GSM (900 MHz) or DAMPS (835 MHz)	No effects	No		Billaudel et al. [2009b]
Cell cycle progression in mouse C3H/10T½ fibroblasts and human U87MG glioblastoma cells	848 or 836 MHz, 0.6 W/kg for 13–100 h	CDMA (848 MHz) or FMCW (836 MHz)	No effects	No		Higashikubo et al. [2001]
Apoptosis, mitochondrial membrane potential, hsp70 level in human peripheral blood mononuclear cells	1800 MHz, 1.4 or 2 W/kg for 44 h (10 min on, 10 min off)	GSM-Basic, GSM-Talk (2/W kg) or GSM DTX (1.4 W/kg)	No effects	No	dRib was used to induce apoptosis	Capri et al. [2004a]
Apoptosis, mitochondrial membrane potential, proliferation, cell cycle in human lymphocytes	900 MHz, 0.070–0.076 W/kg, 1 h/day for 3 days; Additional CW 30 min on/30 min off/30 min on once per day for 3 days	GSM or CW	Decrease of PHA-induced cell proliferation and increase of dRib-induced apoptosis in GSM-exposed cells	Yes		Capri et al. [2004b]
Apoptosis in cdc-48 mutant and wild-type yeast *Saccharomyces cerevisiae*	872 MHz, 3.0 W/kg or 900 MHz, 0.4 W/kg, for 1 h	GSM or CW	GSM exposure increased apoptosis induced by heat and UV radiation in the mutant yeast	Yes	The mutant yeast undergo apoptosis at 37 °C	Markkanen et al. [2004]

Apoptosis, expression of p53-dependent genes involved in apoptosis, p53 expression and phosphorylation in human A172 glioblastoma cells and human IMR-90 foetal lung fibroblasts	2143 MHz, 0.08, 0.25, or 0.8 W/kg, for 24, 28 or 48 h	W-CDMA or CW	No effects	No	Hirose et al. [2006]
Apoptosis in human SH-SY5Y neuroblastoma cells	900 MHz, 0.25 or 2 W/kg for 24 h	GSM (0.25 W/kg) or CW (2 W/kg)	No effects	No	Joubert et al. [2006]
Apoptosis in murine N2a neuroblastoma cells	935 MHz, 3.0 W/kg, for 24 h	GSM-Basic, GSM-Talk or CW	No effects	No	Moquet et al. [2008]
Oxidant levels, antioxidant levels, oxidative damage, nitric oxide production and viability in mouse J774.16 macrophage cells	836 or 848 MHz, 0.8 W/kg for 20–22 h	CDMA (848 MHz) or FMCW (836 MHz)	No effects	No	Cells were stimulated with IFN and LPS to induce oxidative stress	Hook et al. [2004a]
Reduced cellular glutathione levels, lipid peroxidation, proliferation, caspase 3 activity, DNA fragmentation and viability in murine L929 fibroblasts and human SH-SY5Y neuroblastoma cells	872 MHz, 5 W/kg for 1 or 24 h	GSM or CW	Increase of *t*-BOOH-induced lipid peroxidation in SH-SY5Y cells, increase of menadione-induced caspase 3 activity in L929 cells, both after GSM exposure	Yes	Höytö et al. [2008a]
ROS release and hsp70 expression in human umbilical cord blood-derived monocytes and lymphocytes	1800 MHz, 2 W/kg, for 30 or 45 min (continuous or intermittent, 5 min on, 5 min off)	GSM-DTX, GSM-Talk or CW	No effects	No	PMA was used to stimulate ROS production	Lantow et al. [2006a]
Superoxide radical anions, ROS and hsp70 in human Mono Mac 6 and K562 cells	1800 MHz, 0.5–2.0 W/kg, for 45 min	GSM-non-DTX, GSM-DTX, GSM-Talk or CW	No effects	No	PMA and LPS were used to stimulate ROS production	Lantow et al. [2006b]
Superoxide radical anion levels and hsp70 in human Mono Mac 6 cells	1800 MHz, 2.0 W/kg, for 1 h	GSM-non-DTX, GSM or CW	No effects	No	UFP was used to induce stress	Simko et al. [2006]
ROS production in murine L929 fibrosarcoma cells	900 MHz, 0.3 or 1 W/kg, 10 or 30 min	GSM or CW	No effects	No	With or without co-exposure to MX	Zeni et al. [2007]
Neoplastic transformation in mouse fibroblasts	836 or 848 MHz, 0.6 W/kg for 7 or 42 days	CDMA (848 MHz) or FDMA (836 MHz)	No effects	No	Exposure to 4.5 Gy of X-rays before the 42-day exposure	Roti Roti et al. [2001]

dRib, 2-deoxy-D-ribose; DTX, discontinuous transmission; HSP, heat shock proteins; IFN, γ-interferon; LPS, bacterial lipopolysaccharide; MX, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone; ODC, ornithine decarboxylase; P53, protein 53; PMA, phorbol-12-myristate-13-acetate; *t*-BOOH, *tert*-butylhydroperoxide; UFP, ultrafine particles. For other abbreviations, see Tables 1–2.

increased cell proliferation and is increased by many tumour promoters. ODC activity was unaffected in human SH-SY5Y neuroblastoma cells [Höytö et al., 2007a; Billaudel et al., 2009a], murine L929 fibroblasts [Höytö et al., 2006, 2007a,b, 2008b; Billaudel et al., 2009b] and rat C6 glioblastoma cells [Höytö et al., 2007a] exposed to RF energy using various exposure levels and modulation characteristics. Two studies reported effects on ODC activity, but the effects were not dependent on modulation. Höytö et al. [2007a] reported that ODC activity was decreased in rat primary astrocytes after exposure to 872 MHz RF fields, but there were no differences between CW and GSM-modulated signals. Also, there were no differences between CW and Digital Advanced Mobile Phone System (D-AMPS) signals in another study, in which enhancement of ODC activity was observed in L929 cells exposed at 872, but not at 835 MHz in another exposure system [Höytö et al., 2007b].

Several studies have reported no effects on cell proliferation or cell cycle progression from RF energy with various modulation parameters. Antonopoulos et al. [1997] did not find any RF field-related effects on cell cycle progression in human lymphocytes (see Table 2). Higashikubo et al. [2001] reported no effects on cell cycle progression in mouse C3H/10T½ fibroblasts and human U87MG glioblastoma cells, and Höytö et al. [2008a,b] observed no effects on cellular proliferation in L929 and SH-SY5Y cells exposed to RF fields. Zeni et al. [2003] also reported no effects of RF energy on cellular proliferation in human white blood cells. A positive finding was reported by Capri et al. [2004b], who exposed human peripheral blood mononuclear cells (from 8 to 25 healthy donors per condition) stimulated with a mitogen (phytohemagglutinin, 0.1 μl/ml) to 900 MHz RF electromagnetic fields. In cells exposed to GSM-modulated RF fields, a reduced proliferation rate was observed after 72 h in culture. An unmodulated signal did not affect proliferation. The magnitude of the effect on proliferation was small (9%), and cell cycle was not affected at all.

A number of studies have not been able to demonstrate effects on different oxidative stress-related parameters in various cell lines. No effects on oxidant levels, antioxidant levels, oxidative damage or nitric oxide production were detected in mouse J774.16 macrophages exposed to RF fields [Hook et al., 2004a]. Höytö et al. [2008a] reported no effects from RF fields on cellular reduced glutathione levels in L929 and SH-SY5Y cells. Lantow et al. [2006a,b] found no effects on cellular ROS release (measured as reduction of dihydrorhodamine 123 to rhodamine) or superoxide anion radicals (measured as reduction of nitro blue tetrazolium to formazan) in primary human monocytes, human Mono Mac 6, and K562 cells exposed to RF fields, with or without phorbol-12-myristate-13-acetate. Simko et al. [2006] exposed human Mono Mac 6 cells to RF energy and ultrafine particles (<0.1 μm). Exposure to RF fields did not enhance the superoxide anion radical production induced by ultrafine particles. Zeni et al. [2007] exposed murine L929 fibroblasts to RF fields combined with 500 μM 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX). No effects on cellular ROS production (determined using dichlorofluorescein diacetate) were observed from RF field exposure alone or from combined exposure with MX. Two studies have reported positive findings. Lipid peroxidation in SH-SY5Y cells was increased after combined exposure to GSM-modulated RF fields and *t*-butylhydroperoxide, but this effect was not seen in cells exposed to a CW signal [Höytö et al., 2008a]. Luukkonen et al. [2009], in contrast, reported that CW RF fields increased ROS production in SH-SY5Y cells exposed to menadione, but a GSM-modulated signal did not induce a similar response. In later experiments, the same research group did not find any effect of CW or GSM signals on ROS production induced by ferrous chloride [Luukkonen et al., 2010] (both studies by Luukkonen et al. also included measurements of DNA damage and are described in Table 2).

Most of the studies that have addressed effects on apoptosis have found no effects from various modulated and CW RF signals. Capri et al. [2004a] exposed human peripheral blood mononuclear cells to RF fields alone or together with the apoptosis-inducing agent 2-deoxy-D-ribose. No differences were detected between exposed and control cells in apoptosis, as measured by annexin V-FITC staining, or in mitochondrial membrane potential. Also, Hook et al. [2004b] reported that the annexin V-affinity assay did not detect any signs of apoptosis in a human lymphoblastoid leukaemia cell line (Molt-4) exposed to RF fields. Hirose et al. [2006] reported no effects from RF field exposure on annexin V-FITC affinity or expression of apoptosis-related genes in human glioblastoma A172 and human IMR-90 fibroblasts. Höytö et al. [2008b] did not observe any effects on caspase 3 activity in L929 fibroblasts after exposure to RF fields. Joubert et al. [2006] studied the effects of RF fields on apoptosis in human neuroblastoma SH-SY5Y cells and rat primary cortical neurons. No effects on apoptosis were detected with three different techniques (4′,6-diamino-2-phenylindole staining, flow cytometry with TUNEL and PI double staining, and caspase-3 activity). In a recent study, Moquet et al. [2008] did not find any RF field-related effects on cellular apoptosis by annexin V labelling, caspase activation assay and in situ end-labelling in murine

neuroblastoma N2a cells. Effects on apoptosis have been observed in three studies, and they all reported effects from GSM-modulated but not from CW RF fields. All three studies also involved combined exposure to RF fields and apoptosis-inducing agents. Capri et al. [2004b] exposed human lymphocytes from 8 to 25 healthy donors per condition to CW or GSM-modulated 900 MHz RF signals, and found that apoptosis induced by 2-deoxy-D-ribose was increased only by the GSM signal. Markkanen et al. [2004] reported that apoptosis measured by annexin V-FITC staining was enhanced by GSM-modulated RF fields in Cdc-48 mutant yeast cells that were treated with elevated temperature and UV radiation to induce apoptosis. CW RF fields at identical exposure levels did not affect apoptosis. Höytö et al. [2008a] found that caspase 3 activity of L929 cells treated with menadione was increased by exposure to a GSM-modulated RF signal, while a CW signal had no effects.

No effects on neoplastic transformation were seen when mouse C3H/10T½ fibroblasts were exposed to 836 MHz FDMA or 848 MHz CDMA signals [Roti Roti et al., 2001]. The viability of cells has not been found to be affected by any kind of RF fields [Hook et al., 2004a; Höytö et al., 2008a].

In Vitro Studies on Gene and Protein Expression

Studies on gene and protein expression are described in Table 4. A number of studies have addressed effects of RF energy on heat shock proteins. Capri et al. [2004a] investigated hsp70 levels in human peripheral blood mononuclear cells (Table 3); Hirose et al. [2007] studied phosphorylation of hsp27 and heat shock gene expression in human A172 glioblastoma cells and IMR-90 fibroblasts; Lantow et al. [2006a,b] measured hsp70 expression in human umbilical cord blood-derived monocytes and lymphocytes, human Mono Mac 6 and K562 cells (Table 3); Laszlo et al. [2005] used human HeLa S3 cells, hamster ovary HA-1 fibroblasts and C3H/10T½ cells to study the DNA-binding activity of heat shock factor; Lim et al. [2005] measured the number of cells expressing hsp70 or hsp27 in human leukocytes and Simko et al. [2006] studied hsp70 in human Mono Mac 6 cells after combined exposure to RF fields and ultrafine particles. No effects of RF fields were found in any of these studies. Positive findings have been reported in three studies. Czyz et al. [2004] exposed pluripotent wild-type and p53-deficient mouse embryonic stem cells to 1.71 GHz RF fields modulated either by rectangular pulses with a repetition frequency of 217 Hz and a duty cycle of 0.125 (GSM-217), or a signal (GSM-Talk) that simulates a typical phone conversation with temporal changes between GSM-Basic (active during talking phases) and GSM-discontinuous transmission (DTX; active during listening phases) and includes 2 and 8 Hz modulation components in addition to the 217 Hz modulation. The authors reported that hsp70 mRNA was significantly upregulated and transient slight increases were also found in c-jun, c-myc and p21 expression after exposure to the GSM-217 Hz signal. These effects were seen only in the p53-deficient cells, and no responses were observed from exposure to the GSM-Talk signal. The authors concluded that the low frequency components generated by GSM-Talk (2 and 8 Hz) do not promote the effects and that the time-averaged SAR value, which was higher for the GSM-217 than for the GSM-Talk, may be the key reason that determined the biological effects. Franzellitti et al. [2008] found that hsp70C gene product transcription in human HTR-8/SVneo trophoblasts was increased after a 24-h exposure to the GSM-217 Hz signal and reduced after 4 and 6 h exposures to GSM-Talk signals. No effects were seen in cells exposed to CW signals. No effects were seen on many other endpoints (other hsp70 gene products, hsp70 protein expression). It should be noted that, in spite of the multiple endpoints and time points, no correction for multiple testing was applied in the statistical analysis. This increases the likelihood that the few positive findings are due to chance. In experiments with the nematode *Caenorhabditis elegans*, no overall effects were found on hsp16-1 expression from either CW or GSM-modulated RF fields [Dawe et al., 2008]. However, in a post hoc analysis some evidence was found that the expression of hsp16-1 was possibly reduced by about 15% under conditions of moderately elevated background expression in the control worms. The results were similar for modulated and CW exposures.

Large-scale screening for possible responsive genes (transcriptomics) has been used in two studies. Whitehead et al. [2006a,b] performed experiments with C3H/10T½ mouse cells to determine whether FDMA- or CDMA-modulated RF fields can induce changes in gene expression. The exposures had no significant effect on gene expression.

Specific genes other than hsp genes have been addressed in three studies. In different growth phases, mouse-derived C3H/10T½ cells were exposed to CDMA- or FMCW-modulated RF fields. The FMCW signal was frequency modulated and was therefore essentially a CW signal, as there are no variations in amplitude. Significant increases in c-fos mRNA levels were detected after RF field exposure in exponentially growing cells, but there were no differences between the cells exposed to different signals [Goswami et al., 1999]. In a confirmation study, no effects on c-fos

TABLE 4. In Vitro Studies: Gene and Protein Expression

Experimental model	Exposure	Modulation	Findings	Evidence for modulation-specific effect?	Comment	Refs.
Gene expression (RT-PCR, mRNA) in pluripotent embryonic stem (ES) cells, (wild-type and p53-deficient)	1710 MHz, 0.4, 1.5 or 2 W/kg, for 6 or 48 h (on/off cycle: 5/30 min)	GSM-217 (1.5–2 W/kg) or GSM-Talk (0.4 W/kg)	Upregulation of hsp70 RNA levels, and low and transient increase in c-jun, c-myc and p21 levels in p53-deficient ES cells, only in cells exposed to the GSM-217 signal	No (?)	Higher SAR of the GSM-217 signal most likely explains the effects from this signal	Czyz et al. [2004]
DNA-binding activity of heat shock factor in human HeLa S3 cells, hamster ovary HA-1 fibroblasts and mouse C3H/10T½ fibroblasts	836 or 848 MHz, 0.6 or 5 W/kg for 5 min–24 h	FDMA (836 MHz) or CDMA (848 MHz)	No effects	No		Laszlo et al. [2005]
Number of cells expressing hsp70 or hsp27 in human leukocytes (lymphocytes, monocytes)	900 MHz, 0.4, 2.0 or 3.6 W/kg for 20 min, 1 or 4 h	GSM or CW	No effects	No		Lim et al. [2005]
Phosphorylation of hsp27 and heat shock gene expression in human A172 glioblastoma cells and IMR-90 fibroblasts	2143 MHz, 0.08–0.8 W/kg for 2, 24, 28 or 48 h	W-CDMA or CW	No effects	No		Hirose et al. [2007]
hsp70 gene and protein expression in human HTR-8/SV neo trophoblast cells	1800 MHz, 2 W/kg for 4, 16 or 24 h (5 min on, 10 min off)	GSM-217 Hz, GSM-Talk or CW	hsp70C gene product transcription was increased after exposure to GSM-217 Hz for 24 h and decreased after exposure to GSM-Talk for 4 or 16 h	Yes	Many endpoints were measured, but no correction for multiple testing was applied in statistical analysis	Franzellitti et al. [2008]
hsp16-1 gene expression in the nematode Caenorhabditis elegans	1800 MHz, 1.8 W/kg for 2.5 h	GSM or CW	No effects overall; in a post hoc analysis a possible reduction of hsp16-1 expression was observed under conditions where background expression was moderately elevated	No		Dawe et al. [2008]
c-fos, c-jun and c-myc mRNA levels and DNA-binding activity of AP1, AP2 and NF-κB transcription factors in mouse C3H/10T½ fibroblasts	836 or 848 MHz, 0.6 W/kg for 4 days	CDMA (848 MHz) or FMCW (836 MHz)	Significant increases in c-fos mRNA levels were detected in exponentially growing cells	No	Exponentially growing, transitional and plateau phase cells were used	Goswami et al. [1999]
c-fos mRNA levels in mouse C3H/10T½ fibroblasts	836, 848 or 837 MHz, 5 or 10 W/kg, for 4 days	FDMA (836 MHz), CDMA (848 MHz) or TDMA (837 MHz)	No effects	No	Confirmation study of Goswami et al. [1999]	Whitehead et al. [2005]
Gene expression in mouse C3H/10T½ fibroblasts	836 or 848 MHz, 5 W/kg for 24 h	FDMA (836 MHz) or CDMA (848 MHz)	No effects	No		Whitehead et al. [2006a,b]

mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction. For other abbreviations, see Tables 1–3.

mRNA levels were detected in mouse embryo C3H/10T½ fibroblasts [Whitehead et al., 2005]. Hirose et al. [2006] studied the p53-dependent signalling pathways in human A172 and IMR 90 cells exposed to CW or modulated Wideband Code Division Multiple Access (W-CDMA) RF fields (Table 3). No significant differences were found in the expression levels of total p53 and phosphorylated p53 at serine 15 between exposed and sham-exposed cells.

Carcinogenicity: Animal Studies

Only a few animal carcinogenicity studies have used more than one type of RF field (Table 5). No modulation-related or any other tumour-enhancing effects of RF fields were seen in these studies.

Higashikubo et al. [1999] injected 9L gliosarcoma cells into the brains of F-344 male rats after 4 weeks of exposure to 836 MHz FM or 848 MHz CDMA-modulated RF fields. The exposures were continued for 21 weeks after injections. No effects on tumour growth or survival were found.

Zook and Simmens [2001] investigated possible effects of Motorola Integrated Radio Service (MiRS)-modulated or CW 860 MHz fields on neurogenic tumours in the offspring of ethylnitrosourea (ENU)-treated female Sprague–Dawley rats. The rats were exposed to the RF signals until they were killed between the ages of 171 and 325 days. No RF-related effects on the incidence, latency or any other characteristics of neurogenic tumours were observed.

Two-year RF field exposure to a 836 MHz CDMA or a 848 MHz CW signal did not enhance the development of spontaneous brain tumours or tumours in other major organs in Fischer 344 rats [La Regina et al., 2003]. The study investigated whether RF fields increased tumour incidence, and the decreased incidence seen in RF-exposed groups was not statistically tested.

Exposure to 902 MHz GSM-modulated or CW RF fields for 78 weeks was not observed to enhance the development of lymphomas or any other tumours in female CBA/S mice irradiated with X-rays at the beginning of the study [Heikkinen et al., 2001].

Exposure to 902 MHz GSM-modulated or 849 MHz D-AMPS-modulated RF fields did not significantly enhance skin tumourigenesis induced by UV radiation in female ODC transgenic mice or in their non-transgenic littermates [Heikkinen et al., 2003]. The development of tumours was slightly (non-significantly) faster in the exposed than in the control animals, but there was no difference between the two different modulations.

Nervous System: Animal Studies

Studies on nervous system effects in animals are described in Table 6. Fritze et al. [1997b] exposed the heads of rats to simulated GSM and CW signals, and investigated mRNA levels of hsp70, c-fos, c-jun and GFAP. Only CW exposure caused a slight increase in hsp70 mRNA levels immediately or 24 h after exposure. However, this difference is most likely related to the higher SAR in the CW than in the modulated exposure groups. Morrissey et al. [1999] reported that local exposure of the heads of mice to a 1600 MHz Iridium satellite phone signal for 1 h significantly increased c-fos mRNA expression in the forebrain. The findings were consistent with thermal effects, and there were no differences between CW and pulsed exposures.

Persson et al. [1997] reported that exposure of rats to 915 MHz RF fields increased the permeability of the blood–brain barrier to endogenous albumin. The increased permeability was reported to depend on both SAR and frequency of pulse modulation, but most of the exposures used increased the leakage of albumin. CW field exposure was reported to produce a greater effect than pulsed field exposure. Using a head-only exposure system, Fritze et al. [1997a] exposed rats to 900 MHz GSM or CW signals. Small increases in permeability were observed in all treatment groups examined immediately after exposure, and a marked increase in albumin extravasation was present with CW exposure. The SARs in the CW and modulated exposure groups were not, however, comparable in this study, and the effect from CW exposure can be explained by the higher exposure level. Finnie et al. [2002] exposed mice to 900 MHz GSM-modulated or CW fields using long-term, repeated exposure. Small numbers of extravasations were observed in the brains of exposed, sham-exposed and freely moving control animals, but the effects were negligible and did not show any dependence on the modulation used.

Mausset et al. [2001] reported that exposure to a 900 MHz GSM signal at 4 W/kg reduced the content of the neurotransmitter GABA in rat cerebellum. Similar but more pronounced effects were observed following exposure to CW fields at 32 W/kg. The difference is most likely related to the different SAR levels, and suggests involvement of thermal effects.

Nervous System: Human Studies

Studies on nervous system effects in humans are described in Table 7. Several research groups have not found any modulation-specific effects on spontaneous EEG waves. Hietanen et al. [2000] recorded resting EEG from 19 volunteers during sham exposure and

TABLE 5. Animal Carcinogenicity Studies

Experimental model	Exposure	Modulation	Findings	Evidence for modulation-specific effect?	Comment	Refs.
Tumour growth after injection of 9L gliosarcoma cells into brains of male rats	848 or 836 MHz, brain SAR 0.5–1.0 W/kg, 4 h/day, 5 days/week for 25 weeks	CDMA (848 MHz) or CW FM (836 MHz)	Brain mass increased at 848 MHz in rats implanted with highest number of viable cells; no effects on tumour growth or survival	No	The authors concluded the brain mass increase to be related to irregularities in sham-exposed group	Higashikubo et al. [1999]
CNS tumours after transplacental exposure of rat pups to ENU	860 MHz, 0.3–04 W/kg (brain SAR 0.8–1.2 W/kg), 6 h/day, 5 days/week for 22 months	MiRS or CW	No effects	No		Zook and Simmens [2001]
CNS tumours in rats	836 or 848 MHz, brain SAR 1.3 W/kg, 4 h/day, 5 days/week for 104 weeks	FDMA (836 MHz) or CDMA (848 MHz)	No effects	No		La Regina et al. [2003]
Lymphoma in female mice exposed to an initiating dose of X-rays	903 MHz, 1.5 W/kg or 902 MHz, 0.35 W/kg, 1.5 h/days, 5 days/week for 78 weeks	GSM (0.35 W/kg) or NMT (1.5 W/kg)	No effects	No		Heikkinen et al. [2001]
Skin tumours in female mice exposed to repeated doses of UV radiation.	902 MHz or 824 MHz, 0.5 W/kg, 1.5 h/day, 5 days/week for 52 weeks	GSM (902 MHz) or DAMPS (824 MHz)	No effects	No		Heikkinen et al. [2003]

CNS, central nervous system; ENU, *N*-ethyl-*N*-nitrosourea; MiRS, Motorola Integrated Radio Service. For other abbreviations, see Tables 1–4.

TABLE 6. Animal Studies on Nervous System Effects

Experimental model	Exposure	Modulation	Findings	Evidence for modulation-specific effect?	Comment	Refs.
Gene expression and protein levels of hsp70, fos, jun and GFAP in rat brain	900 MHz, 0.3, 1.5 or 7.5 W/kg, 4 h	GSM (0.3 and 1.5 W/kg) or CW (7.5 W/kg)	Slight increase in hsp70 expression at the highest SAR (7.5 W/kg) but no effects on hps70 protein levels or any other exposure-related effects	No (?)	Higher SAR may explain the effect from CW exposure	Fritze et al. [1997b]
Fos mRNA expression in mouse brain	1600 MHz, 0.3–11 W/kg, 1 h	Iridium signal or CW	Increased fos expression	No		Morrissey et al. [1999]
Blood-brain barrier permeability in rat	915 MHz, 0.0004–0.008 to 1.7–8.3 W/kg, 2 min–16 h	Pulsed or CW	Increased albumin permeability	Yes		Persson et al. [1997]
Blood-brain barrier permeability in rat	900 MHz, 0.3, 1.5 or 7.5 W/kg, 4 h	GSM (0.3 and 1.5 W/kg) or CW (7.5 W/kg)	Increased extravasation of albumin immediately after exposure at 7.5 W/kg	No (?)	Higher SAR may explain the effect from CW exposure	Fritze et al. [1997a]
Blood-brain barrier permeability in mouse	900 MHz, 0.25, 1.0, 2.0, or 4.0 W/kg, 1 h/day, 5 days/week for 104 weeks	GSM or CW	Negligible effect	No		Finnie et al. [2002]
GABA content of rat cerebellar tissue	900 MHz, 4 or 32 W/kg, 2 h	GSM (4 W/kg) or CW (32 W/kg)	Decreased stained area in one cell layer following pulsed RF exposure; reduced optical density in three cell layers following CW exposure	No (?)	Stronger effect from the CW exposure is most likely explained by higher SAR	Mausset et al. [2001]

GABA, gamma-aminobutyric acid. For other abbreviations, see Tables 1–5.

TABLE 7. Human Studies on Nervous System Effects

Experimental model	Exposure	Modulation	Findings	Evidence for modulation-specific effect?	Comment	Refs.
Spontaneous EEG	900 or 1800 MHz, mobile phone output power 1–2 W, 20 min	NMT (only 900 MHz) or GSM	No effect, except for difference in absolute (but not relative) power in the delta band in 1 of 4 brain regions with one analogue phone	No		Hietanen et al. [2000]
Spontaneous EEG and cognitive performance	900 MHz, 1/W kg, 30 min	GSM or CW	Increased spectral power at 10.5–11 Hz; reduced reaction speed and increased accuracy in a working memory task after GSM exposure	Yes		Regel et al. [2007]
Spontaneous EEG	900 MHz, 1.56 W/kg, three 15 min exposures during 2 h	GSM or CW	No effects	No		Perentos et al. [2007]
Spontaneous EEG	450 MHz, 0.35 W/kg. 30 min (intermittent, 1 min on, 1 min off)	Pulse modulation at 7, 14 or 21 Hz	Enhancement of EEG power at 14 and 21 Hz modulations; no effect at 7 Hz	Yes	All modulations during one session (3×10 min)	Hinrikus et al. [2008a]
Spontaneous EEG	450 MHz, 0.303 W/kg (1 g average), 20 or 40 min (intermittent, 1 min off, 1 min on)	Pulse modulation at 7, 14, 21, 40, 70, 217 or 1000 Hz	Increased EEG power in alpha and beta bands at 7–217 Hz modulations, but not at 1000 Hz	Yes	Two modulations during one 40 min session	Hinrikus et al. [2008b]
Resting EEG	900 MHz, 0.7 W/kg; 1900 MHz, 1.7 W/kg, 55 min	GSM (900 MHz) or UMTS (1900 MHz)	Enhancement of EEG alpha activity with GSM but not with UMTS modulation	Yes		Croft et al. [2010]
Resting EEG and well-being	900 MHz, 1 W/kg; 1950 MHz, 0.1 or 1 W/kg, 30 min	GSM (900 MHz) or UMTS (1950 MHz)	No effects	No		Kleinlogel et al. [2008b]
Waking and sleep EEG	900 MHz, 1 W/kg (10 g average), 30 min	GSM or CW	EEG alpha activity was increased by the GSM signal; no effect from CW exposure	Yes		Huber et al. [2002]

Sleep EEG	900 MHz, 0.133, 0.015, <0.001 W/kg, 30 min	GSM-Talk (0.133 W/kg), GSM listen (0.015 W/kg) or GSM standby (<0.001 W/kg)	Delayed sleep latency, evident also in 1–4 Hz EEG frontal power after exposure to the talk mode	No (?)	Higher SAR may explain the effect of the talk signal	Hung et al. [2007]
Event-related potentials	902 MHz, 1.1 W/kg (1 g average), 30–40 min	GSM or CW	Some differences in alpha band between GSM and CW exposures, but no significant differences from sham exposure	No (?)	Authors' conclusion: non-existent or subtle effects	Krause et al. [2007]
Event-related potentials	890 MHz, 1.9 W/kg	GSM or CW	No effects	No		Sievert et al. [2005]
Event-related potentials and cognitive performance	900 MHz, 1 W/kg; 1950 MHz, 0.1 or 1 W/kg, 30 min	GSM (900 MHz) or UMTS (1950 MHz)	No effects	No		Kleinlogel et al. [2008a]
Auditory and vestibular functions	882 MHz, 1.3 W/kg, 30 min	GSM or CW	No effects	No		Bamiou et al. [2008]
Regional cerebral blood flow (rCBF)	900 MHz. 1 W/kg (10 g average), 30 min	GSM handset-like or GSM base station-like	Only the handset-like signal affected rCBF	Yes		Huber et al. [2005]
Cognitive performance	915 MHz, 0.125 or 1 W mean power, 25–30 min	GSM (0.125 W) or CW (1 W)	Exposure to the CW signal resulted in decreased choice reaction time	No (?)	Higher SAR may explain the effect of the CW signal	Preece et al. [1999]
Cognitive performance	888 MHz, 1.4 W/kg, 35–40 min	GSM or CW	No effects	No		Russo et al. [2006]
Cognitive performance	888 MHz, 1.4 W/kg, 40 min	GSM or CW	No effects	No		Cinel et al. [2007]
Cognitive performance	902 MHz, 1.1 W/kg, 90 min	GSM or CW	No effects	No		Haarala et al. [2007]

EEG, electroencephalography. For other abbreviations, see Tables 1–6.

exposure to signals from five different mobile handsets (analogue and GSM at 900 and 1800 MHz). Statistical analysis of the EEG revealed an effect in only absolute but not relative power in one frequency band in one of four brain regions studied for only one of the analogue phones. This can be explained as a chance finding. Perentos et al. [2007] studied changes in four specified EEG bands in healthy volunteers exposed to 900 MHz GSM or CW signals. No effect of either type of signal on any EEG band was observed. Kleinlogel et al. [2008b] investigated the effects of GSM- or UMTS-modulated RF fields on resting EEG and well-being in 15 volunteers in a blinded setup. The data provided no evidence of effects of mobile phone signals on the parameters studied.

A few studies have reported modulation-specific effects on spontaneous EEG. Huber et al. [2002] investigated the effects of 900 MHz RF fields on spontaneous EEG using both CW and a signal similar to that emitted by a GSM handset. Power in the alpha band was increased by the GSM but not by the CW exposure. Regel et al. [2007] measured EEG in awake volunteers exposed to 900 MHz GSM or CW signals. An increase in the alpha band activity was observed with the GSM signal, while no effects were seen from the CW signal. Hinrikus et al. [2008b] reported that AM of 450 MHz electromagnetic fields at 14 and 21 Hz enhanced EEG power in the alpha and beta frequencies in healthy volunteers, whereas no effect was detected when the modulation frequency was 7 Hz. The same research group investigated the effect of modulation on resting EEG in individual subjects. They showed that low modulation frequencies (7–217 Hz) caused significant increases in EEG energy for 13–31% of the subjects, but modulation at 1000 Hz was without an effect [Hinrikus et al., 2008a]. Croft et al. [2010] reported that a 900 MHz GSM signal caused alpha frequency enhancement in the resting EEG of adult volunteers, whereas no evidence was found for EEG changes when a 1900 MHz UMTS signal was used. No alpha frequency changes were found in adolescent or elderly volunteers.

Two studies have been published on effects on sleep EEG, and both are positive with respect to modulation-specific effects. Huber et al. [2002] investigated the effects of a handset-like GSM signal or CW exposure at 900 MHz on both sleeping and waking EEG. The GSM-modulated, but not CW exposure, produced a significant increase in the 12.25–13.5 Hz band of EEG. The effects of the GSM-modulated signal, though statistically significant, were small relative to the normal variation in EEG activity during sleep. Hung et al. [2007] studied the effects of 900 MHz RF fields with different components of GSM modulation on sleep onset and sleep architecture. The modulations simulated 'talk' mode (8 and 217 Hz modulations), 'listen' mode (2, 8 and 217 Hz modulations) and 'standby' mode (1–32 Hz modulations), and sham exposure was also included. Delayed sleep latency was observed with 'talk' mode exposure, and this finding was supported by the lack of an increase in EEG power at 1–4 Hz, which is an EEG frequency range particularly sensitive to sleep onset. The authors discuss the possibility that different responses to the 'talk' and 'listen' signals might be explained by differences in the modulation components. However, the exposure levels were different for the three signals, and because all the exposure levels were low (0.133, 0.015 and <0.001 W/kg for 'talk', 'listen' and 'standby', respectively), it might be that only the 'talk' signal exceeded the threshold for any effects.

Sievert et al. [2005] reported lack of effects from exposure of 12 volunteers to CW or GSM signals at 890 MHz on event-related potentials measured before, during and after the exposures. It is not clear whether the study was blinded in any way. Kleinlogel et al. [2008a] reported no effects from GSM- or UMTS-modulated RF fields on event-related potentials in 15 volunteers in a blinded study design.

Krause et al. [2007] reported possible modulation-specific effects on event-related potentials in volunteers exposed to 900 MHz GSM-modulated or CW signals. One group carried out a visual memory task during exposure and the other one, an auditory memory task. No effects on performance were observed from exposure to either type of signal. There were, however, some small but inconsistent differences in EEG power in the alpha band (8–10 Hz) between CW and GSM conditions, but no differences between sham exposure were observed. The authors concluded that EMF effects on the EEG are either non-existent or so prone to many other factors that they are difficult to demonstrate systematically.

Bamiou et al. [2008] studied the effects on auditory and vestibular functions of exposure from a modified handset capable of producing 882 MHz GSM and CW signals. No effects were observed from either sham, CW or GSM signals on the endpoints studied.

Huber et al. [2005] investigated the effects of 900 MHz signals on regional cerebral blood flow (rCBF) using positron emission tomography. Two types of exposure were used: a base station-like and a handset-like signal. Both signals had the same SAR level and same spectral components. However, the base station-like signal had considerably lower power in the main spectral components and was more continuous than the handset-like signal. An increase in rCBF was observed only following the handset-like exposure. The authors

interpreted this finding as supporting their previous observations that pulse modulation of RF fields is necessary to induce changes in brain physiology.

Cinel et al. [2007] exposed 84 healthy volunteers to either an 888 MHz GSM signal or a CW signal. No effect was found on an auditory discrimination task from either signal type. Russo et al. [2006] investigated the effects on cognitive performance of exposure to 888 MHz CW or GSM RF fields using a large number (168) of volunteers. Cognitive performance was studied using several different tasks: reaction time task, 10-choice serial reaction time task, subtraction task, and vigilance task. No significant effects of RF field exposure on task performance were found. Haarala et al. [2007] exposed 36 volunteers to 902 MHz CW or GSM signals, and cognitive functions were assessed using several tasks: simple reaction time, 10-choice reaction time, subtraction, verification, vigilance and memory. No effects were observed for any task from either CW or GSM exposure.

Preece et al. [1999] investigated the performance of 36 volunteers in a wide range of tasks, including short- and long-term memory, simple and choice reaction time, and sustained attention. The volunteers were exposed or sham exposed to a CW or a modulated GSM-type 915 MHz signal. A statistically significant shortening of reaction time during exposure to the CW signal in the choice reaction time task was observed. There was no significant effect of exposure to the pulsed GSM signal. The difference in response to the two signals may be explained by the difference in exposure level, which was eight times higher for the CW signal. Regel et al. [2007] studied reaction time and memory in 20 subjects exposed to a 900 MHz CW or GSM-type signal. No effects were observed in reaction time tests. An improvement in accuracy in the 3-back memory test was found following GSM-type exposure, but not after CW exposure.

Other Studies

Several studies have addressed various biological endpoints that were not included in the paragraphs above. These studies are described in Table 8.

Three in vitro studies have investigated various cellular effects of CW and GSM-modulated RF fields. Cranfield et al. [2001] studied concentration of calcium and calcium signalling patterns in human leukaemic T-cells. No effects were observed from either the modulated or the CW exposures. Platano et al. [2007] measured Ba^{2+} current through voltage-gated calcium channels in primary rat cortical neurons and found no effects, irrespective of the signal used. Thorlin et al. [2006] reported no effects from CW or GSM-modulated RF fields on Il6, Tnfα, Gfap and ED-1 levels in rat primary astroglial and microglial cells.

Three studies have addressed melatonin production in animals. Vollrath et al. [1997] investigated serum melatonin levels and other markers of melatonin synthesis in two strains of rats and in Djungarian hamsters exposed to CW or GSM-modulated 900 MHz fields for up to 6 h. No effects were seen on any of the endpoints examined. This was an exploratory study consisting of many separate experiments. The size of each individual experiment was small, which limits the statistical power to detect any differences. Heikkinen et al. [1999] measured nocturnal 6-hydroxymelationin sulphate excretion in CBA/S mice exposed to RF fields using either a Nordic Mobile Telephony (NMT) or a GSM signal. No effects were observed. Lerchl et al. [2008] exposed adult male Djungarian hamsters to a TETRA-modulated field at 383 MHz or to GSM-modulated fields at 900 or 1800 MHz. No effects were seen on pineal and serum melatonin levels or the weights of testes, brain, kidneys and liver from any of the exposures. A significant transient increase in body mass was observed in animals exposed to the TETRA signal, and a more pronounced (up to 6%) and not transient body mass increase resulted from exposure to the 900 MHz GSM signal. No effect on body mass was seen from exposure to the 1800 MHz GSM signal. The differences in the results seem to be related to differences in frequency rather than modulation. According to the authors' interpretation, the increased body mass results from absorption of RF energy (less energy from food is needed to maintain body temperature), and the differences between the frequencies are related to different absorption patterns (more superficial absorption at 1800 MHz).

Galloni et al. [2005] studied possible effects of RF field exposure on the functioning of the auditory system by measuring distortion product otoacoustic emission (DPOE) in three experiments with different exposure characteristics. In the first experiment, rats were whole-body exposed to a 936 MHz CW field or head-only exposed to a 923 MHz CW field. In the second study, rats were exposed to a 960 MHz GSM field, and in the third study, to a 900 MHz GSM field. No effects on DPOE were found in any of the experiments.

Barker et al. [2007] exposed 120 human volunteers to RF fields and measured blood pressure, heart rate variability and blood catechols (adrenaline and noradrenaline) before and during the exposure. Four different RF signals were applied: GSM modulated, GSM carrier wave, TETRA modulated and TETRA carrier wave. Two sham exposures were done corresponding to the GSM and TETRA exposures. The frequencies of these signals are not described in the

TABLE 8. Studies on Other Effects

Experimental model	Exposure	Modulation	Findings	Evidence for modulation-specific effect?	Comment	Refs.
Concentration of calcium and calcium signalling in human leukaemic T-cells (Jurkat cells)	915 MHz, 2 W/kg, 10 min	GSM or CW	No effects	No		Cranfield et al. [2001]
Ba^{2+} currents through voltage-gated calcium channels in primary rat cortical neurons	900 MHz, 2 W/kg, for 1–3 periods of 90 s	GSM or CW	No effects	No		Platano et al. [2007]
Il6, Tnfα, Gfap and ED1 levels in rat primary astroglial and microglial cells	900 MHz, 27 W/kg, for 24 h or 3 W/kg, 4, 8 or 24 h	GSM or CW	No effects	No		Thorlin et al. [2006]
Pineal seratonin N-acetyltransferase activity, serum melatonin in rats and Djungarian hamsters	900 MHz; 0.06–0.36 W/kg (rats), 0.04 W/kg (hamsters), 15 min–6 h	GSM or CW	No effects	No		Vollrath et al. [1997]
Nocturnal 6-hydroxymelatonin sulphate production in female mice	902 MHz, 1.5 W/kg or 0.35 W/kg for 78 weeks (1.5 h/day, 5 days/week)	GSM (0.35 W/kg) or NMT (1.5 W/kg)	No effects	No		Heikkinen et al. [1999]
Body weight, organ weights (testes, brain, kidneys, liver), pineal and serum melatonin levels in Djungarian hamsters	383, 900 or 1800 MHz, 0.08 W/kg, 24 h/day for 60 days	TETRA (383 MHz) or GSM (900 and 1800 MHz)	Body mass increased at 383 and 900 but not at 1800 MHz; no other effects	No	The differences seem to be related to frequency rather than modulation	Lerchl et al. [2008]
Distortion product otoacoustic emission in rats	900, 923, 936 or 960 MHz, head SAR 1 or 2 W/kg, 2–3 h/day, 5 days/week for 1 or 4 weeks	GSM or CW	No effects	No	GSM and CW experiments were not identical	Galloni et al. [2005]
Blood pressure, heart rate variability and blood catechols in human volunteers	2 W/kg (10 g average), 40 min	GSM, TETRA or CW	No effects	No	Frequencies of the RF signals are not given in the article	Barker et al. [2007]
Subjective symptoms, blood pressure, heart rate and breathing rate in human volunteers with self-reported EMF sensitivity	900 or 1800 MHz, phone output powers of 1, 0.25 and 0.125 W, 30 min	GSM (1800 MHz) or NMT (900 MHz)	No effects	No		Hietanen et al. [2002]
Subjective symptoms in human volunteers with and without self-reported EMF sensitivity	900 MHz, 1.4 W/kg, 50 min	GSM or CW	No effects	No		Rubin et al. [2006]
Subjective symptoms in human volunteers	888 MHz, 1.4 W/kg, 40 min	GSM or CW	No consistent effects (dizziness was increased in 1 of 3 experiments)	No		Cinel et al. [2008]

ED1, marker for reactive microglia; Gfap, glial fibrillary acidic protein; Il6, interleukin 6; Tnfα, tumour necrosis factor alpha. For other abbreviations, see Tables 1–7.

article (but standard TETRA and GSM frequencies were probably used). No effects of any RF signal were found on blood catechol concentrations, mean arterial blood pressure or any measure of heart rate variability. The only statistically significant finding was slightly reduced mean arterial blood pressure during sham GSM exposure.

Three studies have investigated subjective symptoms and/or perception of RF electromagnetic fields in human volunteers. Hietanen et al. [2002] exposed 20 volunteers with self-reported sensitivity to 900 MHz GSM- or NMT-modulated fields or 1800 MHz GSM-modulated fields. Slightly more symptoms were reported during sham exposure than real exposure, and the subjects did not distinguish real exposure from sham exposure. No effects on blood pressure, heart rate or breathing rate were observed. Rubin et al. [2006] studied symptoms among 60 subjects with self-reported sensitivity and 60 'non-sensitive' subjects. The subjects were exposed to GSM-modulated or CW 900 MHz fields. The participants were not able to tell whether the RF field was on or off, and the occurrence of symptoms (which were much more common among the sensitive than the non-sensitive subjects) was independent of the exposure condition. Cinel et al. [2008] exposed three groups of volunteers (a total of 496 subjects) to either GSM or unmodulated signals at 888 MHz. For one group of participants ($n = 160$), it was found that dizziness, which was one of the five specific symptoms rated by the participants, was affected by RF field exposure. However, this was not consistently found in the other two groups of participants. No other significant effects were found.

DISCUSSION

One of the basic principles of science is that findings should be reproducible. Any single positive finding can therefore not be considered as definitive evidence for modulation-specific effects. Reproducibility can be shown by replication of the same results by independent researchers in an identical (as much as possible) experiment. None of the positive studies reviewed here have been replicated in such experiments. However, reproducibility can also be established if studies with non-identical methods consistently point to the same direction, that is, produce independent evidence of the existence of an effect or a phenomenon. This can be considered a stronger form of reproducibility; robust effects do not require exact replication of experimental parameters. In the discussion that follows, the focus is on the second form of reproducibility, that is, consistency between the positive findings.

Most of the studies included in this review have provided no evidence of modulation-specific effects. The majority of these studies were negative for any effects either from modulated or CW RF fields, but there were some studies that reported similar effects from all signals tested. All animal carcinogenicity studies produced negative findings independent of modulation parameters, and only 3 out of 19 genotoxicity studies provided suggestive evidence of modulation-dependent effects. The three positive findings are quite different and do not form a consistent picture: one of them reported some differences between two different modulation types, one reported effects from CW but not GSM-modulated exposure and the third reported effects from phase-modulated but not CW exposure. These isolated results may well be false-positive findings due to chance.

Among the studies on cancer-relevant non-genotoxic endpoints, 3 out of 20 reported modulation-related effects. In all three cases, biological effects (apoptosis, altered cell proliferation, lipid peroxidation) were induced by a pulsed (GSM modulated) signal but not by a CW signal. It is of interest that all positive studies involved combined exposure to RF fields and other agents, and found modulation-specific effects on apoptosis.

There were nine studies on gene and protein expression. Evidence of modulation-dependent effects was found in only one study, which reported effects from pulsed GSM-type signals but not from CW signals.

Of the 18 studies on nervous system effects in human volunteers, one-third ($n = 6$) reported modulation-specific effects. Five studies reported effects on EEG in awake or sleeping subjects, one study reported increased rCBF and one study reported improved performance in a memory test. Concerning effects on the electrical activity of the brain, it is worth noting that increased power in the alpha band (8–12 Hz) of EEG has been consistently seen in several studies. Most of the positive studies have used GSM-type modulation and have found that signals with pulse modulation are more biologically active than CW fields, or that signals with higher degree of modulation (e.g., handset-like signals) are more biologically active than signals with lower degree of modulation (e.g., base station-like signals). Overall, the consistency of the positive findings indicates that there may be reproducible modulation-specific effects on the human central nervous system. It should be noted that only studies involving more than one type of signal (modulated and CW or at least two different modulations) were included in this review. Studies that have used only GSM-type signals have provided additional evidence for effects of

modulated signals on human brain functions [Van Rongen et al., 2009]. The interpretation of the EEG findings is complicated by the presence of conducting EEG electrodes and leads, as they have been shown to enhance the local electromagnetic fields during RF exposure [Angelone et al., 2010].

The animal studies discussed in this review did not provide much support for modulation-dependent effects on the nervous system. However, none of the studies reviewed addressed endpoints similar to those used in the positive human studies (EEG, cerebral blood flow and improved cognitive performance). Kumlin et al. [2007] found that GSM-type modulated RF fields might improve memory and learning in rodents, but no CW signals were used in their study, and it is therefore not possible to conclude whether the effects depend on the presence of modulation.

The positive findings suggesting modulation-specific effects raise the question about biophysical mechanisms that can explain such effects. As discussed by Foster and Repacholi [2004], there is no plausible, generally accepted mechanism for modulation-specific effects at realistic electromagnetic field intensities, and recent findings indicate that demodulation of RF energy (which would increase the plausibility of modulation-dependent effects) does not occur in living cells or tissues [Kowalczuk et al., 2010]. The experimental evidence is strongest for effects on the central nervous system. In further elucidation of the mechanisms, a key question is whether the effects observed reflect interaction of modulated signals with the complex structure and function of the nervous system (which itself generates electrical signals with frequencies close to the modulation frequencies used in experimental studies on bioeffects of RF fields), or whether similar effects can be observed in less complex systems consisting of single cells. From this point of view, it is of high interest to follow-up the few positive in vitro studies because these may represent modulation-dependent effects at the cellular level. There are no systematic data on how the reported modulation-specific effects depend on the level of exposure to RF fields. Most of the positive studies have used SARs of 1–5 W/kg, but modulation-dependent effects on the human central nervous system [Hinrikus et al. 2008a,b; Croft et al., 2010] and in vitro systems [Capri et al., 2004b; Markkanen et al., 2004] have also been reported at levels below 1 W/kg. Systematic data are also lacking concerning dependence of the effects on modulation parameters. Most of the positive studies have used GSM-type signals that include pulses at 217 Hz and possibly some lower frequency (2 and 8 Hz) modulation components. The findings of Hinrikus et al. [2008a,b], however, indicate that pulse modulations from 7 to 217 Hz may also affect human EEG.

CONCLUSIONS

The studies discussed in this review indicate that there may be specific effects from amplitude-modulated RF electromagnetic fields on the human central nervous system. The effects reported (changes in EEG, cerebral blood flow and performance in a memory test) are relatively minor, and do not at present allow conclusions concerning possible adverse health effects. Further studies are warranted to determine how the effects depend on modulation characteristics and exposure level, and to investigate possible mechanisms and relevance to human health. Also, animal studies with suitable experimental models would be valuable to shed light on the mechanisms of the modulation-dependent effects on the central nervous system.

No consistent evidence has been found for modulation-dependent effects on carcinogenesis or genotoxicity. Some in vitro studies have provided suggestive evidence of modulation-specific effects at the cellular level. Follow-up of the positive findings would be helpful for understanding the mechanisms of any specific effects of modulated RF energy.

REFERENCES

Angelone LM, Bit-Babik G, Chou C-K. 2010. Computational electromagnetic analysis in a human head model with EEG electrodes and leads exposed to RF-field sources at 915 MHz and 1748 MHz. Radiat Res 174:91–100.

Antonopoulos A, Eisenbrandt H, Obe G. 1997. Effects of high-frequency electromagnetic fields on human lymphocytes in vitro. Mutat Res 395:209–214.

Bamiou DE, Ceranic B, Cox R, Watt H, Chadwick P, Luxon LM. 2008. Mobile telephone use effects on peripheral audiovestibular function: A case-control study. Bioelectromagnetics 29:108–117.

Barker AT, Jackson PR, Parry H, Coulton LA, Cook GG, Wood SM. 2007. The effect of GSM and TETRA mobile handset signals on blood pressure, catechol levels and heart rate variability. Bioelectromagnetics 28:433–438.

Bawin SM, Kaczmarek LK, Adey WR. 1975. Effects of modulated VHF fields on the central nervous system. Ann N Y Acad Sci 247:74–81.

Belyaev IY, Markova E, Hillert L, Malmgren LOG, Persson BBR. 2009. Microwaves from UMTS/GSM mobile phones induce long-lasting inhibition of 53BP1/gamma-H2AX DNA repair foci in human lymphocytes. Bioelectromagnetics 30:129–141.

Billaudel B, Taxile M, Poulletier de Gannes F, Ruffie G, Lagroye I, Veyret B. 2009a. Effects of exposure to DAMPS and GSM signals on ornithine decarboxylase (ODC) activity: II. SH-SY5Y human neuroblastoma cells. Int J Radiat Biol 85:519–522.

Billaudel B, Taxile M, Ruffie G, Veyret B, Lagroye I. 2009b. Effects of exposure to DAMPS and GSM signals on ornithine decarboxylase (ODC) activity: I. L-929 mouse fibroblasts. Int J Radiat Biol 85:510–518.

Bisht KS, Moros EG, Straube WL, Baty JD, Roti Roti JL. 2002. The effect of 835.62 MHz FDMA or 847.74 MHz CDMA modulated radiofrequency radiation on the induction of micronuclei in C3H 10T(1/2) cells. Radiat Res 157:506–515.

Blackman CF, Benane SG, Elder JA, House DE, Lampe JA, Faulk JM. 1980. Induction of calcium-ion efflux from brain tissue by radiofrequency radiation: Effect of sample number and modulation frequency on the power-density window. Bioelectromagnetics 1:35–43.

Capri M, Scarcella E, Bianchi E, Fumelli C, Mesirca P, Agostini C, Remondini D, Schuderer J, Kuster N, Franceschi C, Bersani F. 2004a. 1800 MHz radiofrequency (mobile phones, different Global System for Mobile Communication modulations) does not affect apoptosis and heat shock protein 70 level in peripheral blood mononuclear cells from young and old donors. Int J Radiat Biol 80:389–397.

Capri M, Scarcella E, Fumelli C, Bianchi E, Salvioli S, Mesirca P, Agostini C, Antolini A, Schiavoni A, Castellani G, Bersani F, Franceschi C. 2004b. In vitro exposure of human lymphocytes to 900 MHz CW and GSM modulated radiofrequency: Studies of proliferation, apoptosis and mitochondrial membrane potential. Radiat Res 162:211–218.

Cinel C, Boldini A, Russo R, Fox E. 2007. Effects of mobile phone electromagnetic fields on an auditory order threshold task. Bioelectromagnetics 28:493–496.

Cinel C, Russo R, Boldini A, Fox E. 2008. Exposure to mobile phone electromagnetic fields and subjective symptoms: A double-blind study. Psychosom Med 70:345–348.

Cranfield CG, Wood AW, Anderson V, Menezes KG. 2001. Effects of mobile phone type signals on calcium levels within human leukaemic T-cells (Jurkat cells). Int J Radiat Biol 77:1207–1217.

Croft RJ, Leung S, McKenzie RJ, Loughran SP, Iskra S, Hamblin DL, Cooper NR. 2010. Effects of 2G and 3G mobile phones on human alpha rhythms: Resting EEG in adolescents, young adults, and the elderly. Bioelectromagnetics 31:434–444.

Czyz J, Guan K, Zeng Q, Nikolova T, Meister A, Schonborn F, Schuderer J, Kuster N, Wobus AM. 2004. High frequency electromagnetic fields (GSM signals) affect gene expression levels in tumor suppressor p53-deficient embryonic stem cells. Bioelectromagnetics 25:296–307.

d'Ambrosio G, Massa R, Scarfi MR, Zeni O. 2002. Cytogenetic damage in human lymphocytes following GMSK phase modulated microwave exposure. Bioelectromagnetics 23:7–13.

Dawe AS, Nylund R, Leszczynski D, Kuster N, Reader T, De Pomerai DI. 2008. Continuous wave and simulated GSM exposure at 1.8 W/kg and 1.8 GHz do not induce hsp 16-1 heat-shock gene expression in *Caenorhabditis elegans*. Bioelectromagnetics 29:92–99.

Diem E, Schwarz C, Adlkofer F, Jahn O, Rudiger H. 2005. Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro. Mutat Res 583: 178–183.

Elder JA, Chou CK. 2003. Auditory response to pulsed radiofrequency energy. Bioelectromagnetics 24 (Suppl 6): S162–S173.

Finnie JW, Blumbergs PC, Manavis J, Utteridge TD, Gebski V, Davies RA, Vernon-Roberts B, Kuchel TR. 2002. Effect of long-term mobile communication microwave exposure on vascular permeability in mouse brain. Pathology 34:344–347.

Foster KR, Repacholi MH. 2004. Biological effects of radiofrequency fields: Does modulation matter? Radiat Res 162:219–225.

Franzellitti S, Valbonesi P, Contin A, Biondi C, Fabbri E. 2008. HSP70 expression in human trophoblast cells exposed to different 1.8 GHz mobile phone signals. Radiat Res 170: 488–497.

Fritze K, Sommer C, Schmitz B, Mies G, Hossmann KA, Kiessling M, Wiessner C. 1997a. Effect of global system for mobile communication (GSM) microwave exposure on blood-brain barrier permeability in rat. Acta Neuropathol 94:465–470.

Fritze K, Wiessner C, Kuster N, Sommer C, Gass P, Hermann DM, Kiessling M, Hossmann KA. 1997b. Effect of global system for mobile communication microwave exposure on the genomic response of the rat brain. Neuroscience 81:627–639.

Galloni P, Lovisolo GA, Mancini S, Parazzini M, Pinto R, Piscitelli M, Ravazzani P, Marino C. 2005. Effects of 900 MHz electromagnetic fields exposure on cochlear cells' functionality in rats: Evaluation of distortion product otoacoustic emissions. Bioelectromagnetics 26:536–547.

Goswami PC, Albee LD, Parsian AJ, Baty JD, Moros EG, Pickard WF, Roti Roti JL, Hunt CR. 1999. Proto-oncogene mRNA levels and activities of multiple transcription factors in C3H 10T 1/2 murine embryonic fibroblasts exposed to 835.62 and 847.74 MHz cellular phone communication frequency radiation. Radiat Res 151:300–309.

Haarala C, Takio F, Rintee T, Laine M, Koivisto M, Revonsuo A, Hamalainen H. 2007. Pulsed and continuous wave mobile phone exposure over left versus right hemisphere: Effects on human cognitive function. Bioelectromagnetics 28:289–295.

Heikkinen P, Kumlin T, Laitinen JT, Komulainen H, Juutilainen J. 1999. Chronic exposure to 50-Hz magnetic fields or 900-MHz electromagnetic fields does not alter nocturnal 6-hydroxymelatonin sulfate secretion in CBA/S mice. Electro- and Magnetobiology 18:33–42.

Heikkinen P, Kosma VM, Hongisto T, Huuskonen H, Hyysalo P, Komulainen H, Kumlin T, Lahtinen T, Lang S, Puranen L, Juutilainen J. 2001. Effects of mobile phone radiation on X-ray-induced tumorigenesis in mice. Radiat Res 156:775–785.

Heikkinen P, Kosma VM, Alhonen L, Huuskonen H, Komulainen H, Kumlin T, Laitinen JT, Lang S, Puranen L, Juutilainen J. 2003. Effects of mobile phone radiation on UV-induced skin tumourigenesis in ornithine decarboxylase transgenic and non-transgenic mice. Int J Radiat Biol 79:221–233.

Hietanen M, Kovala T, Hamalainen AM. 2000. Human brain activity during exposure to radiofrequency fields emitted by cellular phones. Scand J Work Environ Health 26:87–92.

Hietanen M, Hamalainen AM, Husman T. 2002. Hypersensitivity symptoms associated with exposure to cellular telephones: No causal link. Bioelectromagnetics 23:264–270.

Higashikubo R, Culbreth VO, Spitz DR, LaRegina MC, Pickard WF, Straube WL, Moros EG, Roti JL. 1999. Radiofrequency electromagnetic fields have no effect on the in vivo proliferation of the 9L brain tumor. Radiat Res 152:665–671.

Higashikubo R, Ragouzis M, Moros EG, Straube WL, Roti Roti JL. 2001. Radiofrequency electromagnetic fields do not alter the cell cycle progression of C3H 10T and U87MG cells. Radiat Res 156:786–795.

Hinrikus H, Bachmann M, Lass J, Karai D, Tuulik V. 2008a. Effect of low frequency modulated microwave exposure on human

EEG: Individual sensitivity. Bioelectromagnetics 29:527–538.

Hinrikus H, Bachmann M, Lass J, Tomson R, Tuulik V. 2008b. Effect of 7, 14 and 21 Hz modulated 450 MHz microwave radiation on human electroencephalographic rhythms. Int J Radiat Biol 84:69–79.

Hirose H, Sakuma N, Kaji N, Suhara T, Sekijima M, Nojima T, Miyakoshi J. 2006. Phosphorylation and gene expression of p53 are not affected in human cells exposed to 2.1425 GHz band CW or W-CDMA modulated radiation allocated to mobile radio base stations. Bioelectromagnetics 27:494–504.

Hirose H, Sakuma N, Kaji N, Nakayama K, Inoue K, Sekijima M, Nojima T, Miyakoshi J. 2007. Mobile phone base station-emitted radiation does not induce phosphorylation of Hsp27. Bioelectromagnetics 28:99–108.

Hook GJ, Spitz DR, Sim JE, Higashikubo R, Baty JD, Moros EG, Roti Roti JL. 2004a. Evaluation of parameters of oxidative stress after in vitro exposure to FMCW- and CDMA-modulated radiofrequency radiation fields. Radiat Res 162:497–504.

Hook GJ, Zhang P, Lagroye I, Li L, Higashikubo R, Moros EG, Straube WL, Pickard WF, Baty JD, Roti Roti JL. 2004b. Measurement of DNA damage and apoptosis in Molt-4 cells after in vitro exposure to radiofrequency radiation. Radiat Res 161:193–200.

Höytö A, Sihvonen AP, Alhonen L, Juutilainen J, Naarala J. 2006. Modest increase in temperature affects ODC activity in L929 cells: Low-level radiofrequency radiation does not. Radiat Environ Biophys 45:231–235.

Höytö A, Juutilainen J, Naarala J. 2007a. Ornithine decarboxylase activity is affected in primary astrocytes but not in secondary cell lines exposed to 872 MHz RF radiation. Int J Radiat Biol 83:367–374.

Höytö A, Juutilainen J, Naarala J. 2007b. Ornithine decarboxylase activity of L929 cells after exposure to continuous wave or 50 Hz modulated radiofrequency radiation—A replication study. Bioelectromagnetics 28:501–508.

Höytö A, Luukkonen J, Juutilainen J, Naarala J. 2008a. Proliferation, oxidative stress and cell death in cells exposed to 872 MHz radiofrequency radiation and oxidants. Radiat Res 170:235–243.

Höytö A, Sokura M, Juutilainen J, Naarala J. 2008b. Radiofrequency radiation does not significantly affect ornithine decarboxylase activity, proliferation, or caspase-3 activity of fibroblasts in different physiological conditions. Int J Radiat Biol 84:727–733.

Huber R, Treyer V, Borbely AA, Schuderer J, Gottselig JM, Landolt HP, Werth E, Berthold T, Kuster N, Buck A, Achermann P. 2002. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res 11:289–295.

Huber R, Treyer V, Schuderer J, Berthold T, Buck A, Kuster N, Landolt HP, Achermann P. 2005. Exposure to pulse-modulated radio frequency electromagnetic fields affects regional cerebral blood flow. Eur J Neurosci 21:1000–1006.

Hung CS, Anderson C, Horne JA, McEvoy P. 2007. Mobile phone 'talk-mode' signal delays EEG-determined sleep onset. Neurosci Lett 421:82–86.

International Commission on Non-Ionizing Radiation Protection (ICNIRP). 2009. Exposure to high frequency electromagnetic fields, biological effects and health consequences (100 kHz–300 GHz). ICNIRP 16/2009. http://www.icnirp.de/documents/RFReview.pdf (last accessed 19 December 2010).

Joubert V, Leveque P, Rametti A, Collin A, Bourthoumieu S, Yardin C. 2006. Microwave exposure of neuronal cells in vitro: Study of apoptosis. Int J Radiat Biol 82:267–275.

Juutilainen J, de Seze R. 1998. Biological effects of amplitude-modulated radiofrequency radiation. Scand J Work Environ Health 24:245–254.

Juutilainen J, Heikkinen P, Soikkeli H, Maki-Paakkanen J. 2007. Micronucleus frequency in erythrocytes of mice after long-term exposure to radiofrequency radiation. Int J Radiat Biol 83:213–220.

Kleinlogel H, Dierks T, Koenig T, Lehmann H, Minder A, Berz R. 2008a. Effects of weak mobile phone—electromagnetic fields (GSM, UMTS) on event related potentials and cognitive functions. Bioelectromagnetics 29:488–497.

Kleinlogel H, Dierks T, Koenig T, Lehmann H, Minder A, Berz R. 2008b. Effects of weak mobile phone-electromagnetic fields (GSM, UMTS) on well-being and resting EEG. Bioelectromagnetics 29:479–487.

Komatsubara Y, Hirose H, Sakurai T, Koyama S, Suzuki Y, Taki M, Miyakoshi J. 2005. Effect of high-frequency electromagnetic fields with a wide range of SARs on chromosomal aberrations in murine m5S cells. Mutat Res 587:114–119.

Kowalczuk C, Yarwood G, Blackwell R, Priestner M, Sienkiewicz Z, Bouffler S, Ahmed I, Abd-Alhameed R, Excell P, Hodzic V, Davis C, Gammon R, Balzano Q. 2010. Absence of non-linear responses in cells and tissues exposed to RF energy at mobile phone frequencies using a doubly resonant cavity. Bioelectromagnetics 31:556–565.

Krause CM, Pesonen M, Haarala Bjornberg C, Hamalainen H. 2007. Effects of pulsed and continuous wave 902 MHz mobile phone exposure on brain oscillatory activity during cognitive processing. Bioelectromagnetics 28:296–308.

Kumlin T, Iivonen H, Miettinen P, Juvonen A, van Groen T, Puranen L, Pitkäaho R, Juutilainen J, Tanila H. 2007. Mobile phone radiation and the developing brain: Behavioral and morphological effects in juvenile rats. Radiat Res 168:471–479.

La Regina M, Moros EG, Pickard WF, Straube WL, Baty J, Roti Roti JL. 2003. The effect of chronic exposure to 835.62 MHz FDMA or 847.74 MHz CDMA radiofrequency radiation on the incidence of spontaneous tumors in rats. Radiat Res 160:143–151.

Lantow M, Lupke M, Frahm J, Mattsson MO, Kuster N, Simko M. 2006a. ROS release and Hsp70 expression after exposure to 1,800 MHz radiofrequency electromagnetic fields in primary human monocytes and lymphocytes. Radiat Environ Biophys 45:55–62.

Lantow M, Schuderer J, Hartwig C, Simko M. 2006b. Free radical release and HSP70 expression in two human immune-relevant cell lines after exposure to 1800 MHz radiofrequency radiation. Radiat Res 165:88–94.

Laszlo A, Moros EG, Davidson T, Bradbury M, Straube W, Roti Roti J. 2005. The heat-shock factor is not activated in mammalian cells exposed to cellular phone frequency microwaves. Radiat Res 164:163–172.

Lerchl A, Wilhelm AF. 2010. Critical comments on DNA breakage by mobile-phone electromagnetic fields [Diem et al., Mutat. Res. 583 (2005) 178–183]. Mutat Res 697:60–65.

Lerchl A, Kruger H, Niehaus M, Streckert JR, Bitz AK, Hansen V. 2008. Effects of mobile phone electromagnetic fields at non-thermal SAR values on melatonin and body weight of Djungarian hamsters (Phodopus sungorus). J Pineal Res 44:267–272.

Li L, Bisht KS, LaGroye I, Zhang P, Straube WL, Moros EG, Roti Roti JL. 2001. Measurement of DNA damage in mammalian

cells exposed in vitro to radiofrequency fields at SARs of 3–5 W/kg. Radiat Res 156:328–332.

Lim HB, Cook GG, Barker AT, Coulton LA. 2005. Effect of 900 MHz electromagnetic fields on nonthermal induction of heat-shock proteins in human leukocytes. Radiat Res 163:45–52.

Luukkonen J, Hakulinen P, Maki-Paakkanen J, Juutilainen J, Naarala J. 2009. Enhancement of chemically induced reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells by 872 MHz radiofrequency radiation. Mutat Res 662:54–58.

Luukkonen J, Juutilainen J, Naarala J. 2010. Combined effects of 872 MHz radiofrequency radiation and ferrous chloride on reactive oxygen species production and DNA damage in human SH-SY5Y neuroblastoma cells. Bioelectromagnetics 31:417–424.

Maes A, Collier M, Verschaeve L. 2001. Cytogenetic effects of 900 MHz (GSM) microwaves on human lymphocytes. Bioelectromagnetics 22:91–96.

Malyapa RS, Ahern EW, Straube WL, Moros EG, Pickard WF, Roti Roti JL. 1997. Measurement of DNA damage after exposure to electromagnetic radiation in the cellular phone communication frequency band (835.62 and 847.74 MHz). Radiat Res 148:618–627.

Markkanen A, Penttinen P, Naarala J, Pelkonen J, Sihvonen A-P, Juutilainen J. 2004. Apoptosis induced by ultraviolet radiation is enhanced by amplitude modulated radiofrequency radiation in mutant yeast cells. Bioelectromagnetics 25:127–133.

Mausset AL, de Seze R, Montpeyroux F, Privat A. 2001. Effects of radiofrequency exposure on the GABAergic system in the rat cerebellum: Clues from semi-quantitative immunohistochemistry. Brain Res 912:33–46.

McNamee JP, Bellier PV, Gajda GB, Lavallee BF, Marro L, Lemay E, Thansandote A. 2003. No evidence for genotoxic effects from 24 h exposure of human leukocytes to 1.9 GHz radiofrequency fields. Radiat Res 159:693–697.

Moquet J, Ainsbury E, Bouffler S, Lloyd D. 2008. Exposure to low level GSM 935 MHZ radiofrequency fields does not induce apoptosis in proliferating or differentiated murine neuroblastoma cells. Radiat Prot Dosimetry 131:287–296.

Morrissey JJ, Raney S, Heasley E, Rathinavelu P, Dauphinee M, Fallon JH. 1999. IRIDIUM exposure increases c-fos expression in the mouse brain only at levels which likely result in tissue heating. Neuroscience 92:1539–1546.

NCRP. 2003. NCRP Commentary No. 18, Biological Effects of Modulated Radiofrequency Fields. National Council on Radiation Protection and Measurements. http://www.ncrponline.org/Publications/Commentaries/Comm18press.html (last accessed 19 December 2010).

Pakhomov AG, Mathur SP, Doyle J, Stuck BE, Kiel JL, Murphy MR. 2000. Comparative effects of extremely high power microwave pulses and a brief CW irradiation on pacemaker function in isolated frog heart slices. Bioelectromagnetics 21:245–254.

Pakhomov AG, Gajšek P, Allen L, Stuck BE, Murphy MR. 2002. Comparison of dose dependences for bioeffects of continuous-wave and high-peak power microwave emissions using gel-suspended cell cultures. Bioelectromagnetics 23:158–167.

Pakhomov AG, Doyle J, Stuck BE, Murphy MR. 2003. Effects of high-power microwave pulses on synaptic transmission and long term potentiation in hippocampus. Bioelectromagnetics 24:174–181.

Perentos N, Croft RJ, McKenzie RJ, Cvetkovic D, Cosic I. 2007. Comparison of the effects of continuous and pulsed mobile phone like RF exposure on the human EEG. Australas Phys Eng Sci Med 30:274–280.

Persson BR, Salford LG, Brun A. 1997. Blood-brain barrier permeability in rats exposed to electromagnetic fields used in wireless communication. Wireless Netw 3:455–461.

Phillips JL, Ivaschuk O, Ishida-Jones T, Jones RA, Campbell-Beachler M, Haggren W. 1998. DNA damage in Molt-4 T-lymphoblastoid cells exposed to cellular telephone radiofrequency fields in vitro. Bioelectrochem Bioenerg 45:103–110.

Platano D, Mesirca P, Paffi A, Pellegrino M, Liberti M, Apollonio F, Bersani F, Aicardi G. 2007. Acute exposure to low-level CW and GSM-modulated 900 MHz radiofrequency does not affect Ba 2+ currents through voltage-gated calcium channels in rat cortical neurons. Bioelectromagnetics 28:599–607.

Preece AW, Iwi G, Davies-Smith A, Wesnes K, Butler S, Lim E, Varey A. 1999. Effect of a 915-MHz simulated mobile phone signal on cognitive function in man. Int J Radiat Biol 75:447–456.

Regel SJ, Gottselig JM, Schuderer J, Tinguely G, Retey JV, Kuster N, Landolt HP, Achermann P. 2007. Pulsed radio frequency radiation affects cognitive performance and the waking electroencephalogram. Neuroreport 18:803–807.

Roti Roti JL, Malyapa RS, Bisht KS, Ahern EW, Moros EG, Pickard WF, Straube WL. 2001. Neoplastic transformation in C3H 10T(1/2) cells after exposure to 835.62 MHz FDMA and 847.74 MHz CDMA radiations. Radiat Res 155:239–247.

Rubin GJ, Hahn G, Everitt BS, Cleare AJ, Wessely S. 2006. Are some people sensitive to mobile phone signals? Within participants double blind randomised provocation study. BMJ 332:886–891.

Russo R, Fox E, Cinel C, Boldini A, Defeyter MA, Mirshekar-Syahkal D, Mehta A. 2006. Does acute exposure to mobile phones affect human attention? Bioelectromagnetics 27: 215–220.

Sakuma N, Komatsubara Y, Takeda H, Hirose H, Sekijima M, Nojima T, Miyakoshi J. 2006. DNA strand breaks are not induced in human cells exposed to 2.1425 GHz band CW and W-CDMA modulated radiofrequency fields allocated to mobile radio base stations. Bioelectromagnetics 27:51–57.

Sievert U, Eggert S, Pau HW. 2005. Can mobile phone emissions affect auditory functions of cochlea or brain stem? Otolaryngol Head Neck Surg 132:451–455.

Simko M, Hartwig C, Lantow M, Lupke M, Mattsson MO, Rahman Q, Rollwitz J. 2006. Hsp70 expression and free radical release after exposure to non-thermal radio-frequency electromagnetic fields and ultrafine particles in human Mono Mac 6 cells. Toxicol Lett 161:73–82.

Thorlin T, Rouquette JM, Hamnerius Y, Hansson E, Persson M, Bjorklund U, Rosengren L, Ronnback L, Persson M. 2006. Exposure of cultured astroglial and microglial brain cells to 900 MHz microwave radiation. Radiat Res 166:409–421.

Tice RR, Hook GG, Donner M, McRee DI, Guy AW. 2002. Genotoxicity of radiofrequency signals. I. Investigation of DNA damage and micronuclei induction in cultured human blood cells. Bioelectromagnetics 23:113–126.

Van Rongen E, Saunders R, Croft R, Juutilainen J, Lagroye I, Miyakoshi J, de Seze R, Tenforde T, Verschaeve L, Veyret B, Xu Z. 2009. Effects of radiofrequency electromagnetic fields on the human nervous system. J Toxicol Environ Health B Crit Rev 12:572–597.

Vijayalaxmi. 2006. Cytogenetic studies in human blood lymphocytes exposed in vitro to 2.45 GHz or 8.2 GHz radiofrequency radiation. Radiat Res 166:532–538.

Vollrath L, Spessert R, Kratzsch T, Keiner M, Hollmann H. 1997. No short-term effects of high-frequency electromagnetic fields on the mammalian pineal gland. Bioelectromagnetics 18: 376–387.

Whitehead TD, Brownstein BH, Parry JJ, Thompson D, Cha BA, Moros EG, Rogers BE, Roti Roti JL. 2005. Expression of the proto-oncogene fos after exposure to radiofrequency radiation relevant to wireless communications. Radiat Res 164:420–430.

Whitehead TD, Moros EG, Brownstein BH, Roti Roti JL. 2006a. The number of genes changing expression after chronic exposure to code division multiple access or frequency DMA radiofrequency radiation does not exceed the false-positive rate. Proteomics 6:4739–4744.

Whitehead TD, Moros EG, Brownstein BH, Roti Roti JL. 2006b. Gene expression does not change significantly in C3H 10T(1/2) cells after exposure to 847.74 CDMA or 835.62 FDMA radiofrequency radiation. Radiat Res 165:626–635.

Zeni O, Chiavoni AS, Sannino A, Antolini A, Forigo D, Bersani F, Scarfi MR. 2003. Lack of genotoxic effects (micronucleus induction) in human lymphocytes exposed in vitro to 900 MHz electromagnetic fields. Radiat Res 160:152–158.

Zeni O, Di Pietro R, d'Ambrosio G, Massa R, Capri M, Naarala J, Juutilainen J, Scarfi MR. 2007. Formation of reactive oxygen species in L929 cells after exposure to 900 MHz RF radiation with and without co-exposure to 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone. Radiat Res 167:306–311.

Zook BC, Simmens SJ. 2001. The effects of 860 MHz radiofrequency radiation on the induction or promotion of brain tumors and other neoplasms in rats. Radiat Res 155:572–583.