C A N A D A

PROVINCE OF QUEBEC

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RÉGIE DE L'ÉNERGIE / ENERGY BOARD

AUTHORIZATION OF AN INVESTMENT BY HYDRO-QUEBEC DISTRIBUTION – ADVANCED METERING PROJECT PHASE 1

HYDRO-QUEBEC
As Electricity Distributor

Petitioner

-and-

STRATEGIES ENERGETIQUES (S.E.) / ENERGY STRATEGIES (E.S.)

ASSOCIATION QUEBECOISE DE LUTTE CONTRE LA POLLUTION ATMOSPHERIQUE (AQLPA) / QUEBEC ASSOCIATION TO FIGHT AGAINST AIR POLLUTION

Interveners

UNITED KINGDOM HEALTH PROTECTION AGENCY'S INDEPENDENT ADVISORY GROUP ON NON-IONISING RADIATION (AGNIR)

Health Effects from Radiofrequency Electromagnetic Fields. Report to United Kingdom Health Protection Agency.

April 2012.

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Health Effects from Radiofrequency Electromagnetic Fields

Report of the independent Advisory Group on Non-ionising Radiation

Documents of the Health Protection Agency
Radiation, Chemical and Environmental Hazards
April 2012

Contents

3 Cellular Studies

Studies of isolated cellular (*in vitro*) systems have some major advantages over experimental animal or human studies. The main advantage is that they can study simplified systems and allow the RF field exposure conditions and the biological conditions to be more precisely defined and controlled. They also allow a wide variety of different cell types with diverse functions to be tested. One particular cell type that has been used quite frequently is the human lymphocyte; these white blood cells can be easily isolated from blood samples. The isolated cell approach has the benefit that it can produce rapid results, highlight potential areas for further investigation and give an insight into possible mechanisms involved in the interaction. However, these studies have their limitations. The main disadvantage is that isolated cells do not experience the many interactions that would normally take place in a whole organism and hence their response to stimuli is not necessarily the same as it would be in an experimental animal or human.

Cells continually respond to their environment, but when the normal physiological conditions are exceeded and the cells are pushed beyond their capability to adapt problems may occur. Even then, adverse cellular changes may not be harmful to the whole organism as organisms have protection and repair mechanisms. Hence a cellular change does not imply an effect on the whole organism and neither a change at the cellular level nor a change of the whole organism necessarily results in a health effect.

A particular concern is the possibility that exposure to RF fields from mobile phones and base stations is carcinogenic. Carcinogenesis at the cellular level is a multistage process and if exposure to RF fields is involved it would have an effect on one or more of these cellular stages. Most of the known carcinogens, but not all, are genotoxic, that is they cause DNA or chromosomal damage and, therefore, if exposure to RF fields was carcinogenic it could possibly have genotoxic effects on cells. Many of the studies test for genotoxicity and use a range of *in vitro* tests to investigate this possibility. Some studies also test the possibility that RF field exposure contributes by non-genotoxic mechanisms or acts synergistically with other known cancer agents to enhance or promote their effect.

As already mentioned, a major advantage of *in vitro* systems is that the exposure conditions can be controlled and more easily defined than those used in experimental animal or human studies. Most experimental studies use purpose-designed exposure systems in which the relevant parameters can be selected or measured; however, some studies use a mobile phone as the exposure source; the problems associated with this approach have been highlighted in Chapter 2. An important parameter, the specific (energy) absorption rate (SAR), can only be measured indirectly or calculated. The pattern of SAR distribution can vary substantially within an exposure system and no system provides a completely uniform distribution when there are cells present. The type of exposure system – for example, TEM cell or waveguide – will have a major influence on the overall uniformity of the SAR distribution, but other factors, such as the geometry of the container enclosing the cells and even the presence of a meniscus, will alter the pattern of the SAR distribution. Thus, in any exposure system the cells will receive a range of SAR values.

TABLE 3.1 Genotoxic effects

Study	Cellular system	Exposure conditions	Genotoxic effect and measure
Zeni et al, 2005	Leukocytes (h)	900 MHz, 0.3–1 W kg^{-1}, 2 h	No, comet, chromosomal aberration, sister chromsome exchange
Sannino et al, 2006	Leukocytes (h)	1950 MHz, 0.5–2 W kg^{-1}, 24 h	No, comet
Chen et al, 2009	Leukocytes (h)	1800 MHz, 2 W kg^{-1}, 24 h, 5 min on/10 min off	No, comet No synergy with X-rays
Zeni et al, 2008	Lymphocytes (h)	1950 MHz, 2.2 W kg^{-1}, 68 h	No, comet
Stronati et al, 2006	Lymphocytes (h)	935 MHz, 1–2 W kg^{-1}, 24 h	No, comet, chromosomal aberration, sister chromosome exchange, micronucleus No synergy with X-rays
Wang B et al, 2005	Lymphocytes (h)	1800 MHz, 3 W kg^{-1}, 2 h	No, comet Yes, synergy with chemical carcinogens
Gajski and Garaj-Vrhovac, 2009	Lymphocytes (r)	915 MHz, 0.6 W kg^{-1}, 30 min	Yes, comet, bee venom protective
Hansteen et al, 2009	Lymphocytes (h)	2.3 GHz, 10 W m^{-2}, duration?, CW, pulsed	No, chromosomal aberrations
Vijayalaxmi, 2006	Lymphocytes (h)	2.45 GHz, 2.13 W kg^{-1}, 2 h	No, chromosomal aberration, micronucleus
Manti et al, 2008	Lymphocytes (h)	1950 MHz, 0.5–2 W kg^{-1}, 24 h	No, chromosomal aberration, but increased number per cell Yes, synergy with X-rays
Sarimov et al, 2004	Lymphocytes (h)	900 MHz, 5.4 mW kg^{-1}, 30 min	Yes, chromosomal conformation
Markova et al, 2005	Lymphocytes (h)	890–915 MHz, 37 mW kg^{-1}, 1 h	Yes, chromosomal conformation
Mazor et al, 2008	Lymphocytes (h)	800 MHz, 2.9–4.1 W kg^{-1}, 72 h	Yes, chromosomal aneuploidy
McNamee et al, 2003	Lymphocytes (h)	1900 MHz, 0–10 W kg^{-1}, 24 h	No, micronucleus
Zeni et al, 2003	Lymphocytes (h)	1900 MHz, <1.6 W kg^{-1}, 1 h/day, 3 days	No, micronucleus
Scarfi et al, 2006	Lymphocytes (h)	900 MHz, 0–10 W kg^{-1}, 24 h	No, micronucleus
Zotti-Martelli et al, 2005	Lymphocytes (h)	1800 MHz, 5–20 mW cm^{-2}, 3 h	Yes, micronucleus

TABLE 3.1 *Continued*

Study	Cellular system	Exposure conditions	Genotoxic effect and measure
Sannino et al, 2009b	Lymphocytes (h)	900 MHz, peak 10 W kg^{-1}, 20 h	Yes, micronucleus decreased in responders ($n = 4$, total $n = 5$) after mitomycin C
Chen et al, 2010	B-cell lymphoblastoid cells (h)	1800 MHz, 2 W kg^{-1}, up to 24 h	No, comet, synergistic with doxorubicin?
Tiwari et al, 2008	Whole blood (h)	835 MHz, 1.17 W kg^{-1}, 1 or 2 h	No, comet, but effect on DNA repair
Kim et al, 2008	Leukaemia cells (L5178Y) (m), CHL cells	835 MHz, 4 W kg^{-1}, <48 h	No, comet, chromosomal aberration Yes, synergy with chemical carcinogens
Port et al, 2003	Leukaemia cells (HL60)	400 MHz, 500 V cm^{-1}, 6 min	No, micronucleus, apoptosis, gene expression
Campisi et al, 2010	Astroglial cell (r)	900 MHz, 0.26 W m^{-2}, 5, 10 or 20 min, CW, pulsed	Yes, comet, ROS after 20 minutes
Miyakoshi et al, 2002	Glioma (h) (MO54 cells)	2.45 GHz, up to 100 W kg^{-1}, 2 h	No, DNA damage No, single strand breaks
Luukkonen et al, 2010	Neuroblastoma (SH-ST5Y cells)	872 MHz, 5 W kg^{-1}, 1 or 3 h, CW, pulsed	No, comet, cell viability, ROS with or without ferric ions
Sun et al, 2006	Epithelial cells (h)	1800 MHz, 1–3 W kg^{-1}, 2 h	Yes, comet at 3 W kg^{-1}
Yao et al, 2008b	Epithelial cells (h)	1800 MHz, 1–4 W kg^{-1}, 24 h	Yes, comet, H2AX No apoptosis *(paper retracted)*
Yao et al, 2008a	Epithelial cells (h)	1800 MHz, 1–4 W kg^{-1}, 2 h	Yes, comet, H2AX
Shckorbatov et al, 2009	Epithelial cells (h)	35 GHz, 30 μW cm^{-2},10 s	Yes, chromosomal aberration
Sannino et al, 2009a	Fibroblasts (h)	900 MHz, 1 W kg^{-1}, 24 h	No, comet, micronucleus, with or without mutagen
Diem et al, 2005	Fibroblasts (h)	1800 MHz, 1–2 W kg^{-1}, 16 h	Yes, comet
Schwarz et al, 2008	Fibroblasts (h)	1950 MHz, <2 W kg^{-1}, 4–24 h	Yes, comet, micronucleus No, effect on lymphocytes
Speit et al, 2007	Fibroblasts (h) (v79) (hamster)	1800 MHz, 2 W kg^{-1}, 24 h	No, comet, micronucleus Replication study
Markova et al, 2010	Fibroblasts (h) mesenchymal stem cells	905, 915 or 1947 MHz, 37 mW kg^{-1}, 1, 2 or 3 h, or 1 h/day, 5 days/week or 2 weeks	Yes, (but not 905 MHz) DNA double strand breaks

TABLE 3.1 *Continued*

Study	Cellular system	Exposure conditions	Genotoxic effect and measure
Hirose et al, 2006	Fibroblasts (h) (IMR-90), glioma (h) (A172 cells)	2.14 GHz, <800 mW kg^{-1}, 24, 28 or 48 h	No, DNA damage
Sakuma et al, 2006	Fibroblasts (h) (IMR-90), glioma (h) (A172 cells)	2.14 GHz, <800 mW kg^{-1}, 2–24 h	No, DNA damage
Komatsubara et al, 2005	Fibroblasts (m) (m5S cells)	2.45 GHz, <100 W kg^{-1}, 2 h	No, chromosomal aberration
Hirose et al, 2008	Fibroblasts (m) (BALB/3T3 cells)	2.14 GHz, 80–800 mW kg^{-1}, 6 weeks	No, cell transformation
Wang J et al, 2005	Fibroblasts (m) (C3H10T½)	2.45 GHz, 5–200 W kg^{-1}, 2 h	No, used tumour promoters, cell transformation
Valbonesi et al, 2008	Trophoblast (h) (HTR-8/SV neo)	1817 MHz, 2 W kg^{-1}, 1 h, pulsed	No, comet, proliferation, stress
Franzellitti et al, 2010	Trophoblast (h) (HTR-8/SV neo)	1800 MHz, 2 W kg^{-1}, 4, 16 or 24 h, 5 min on/10 min off, CW, pulsed	Yes, comet, transient increase with pulsed
Huang et al, 2008	Auditory hair cells (m)	1763 MHz, 20 W kg^{-1}, 24–48 h	No, comet, DNA, stress
Koyama et al, 2004	Ovary cells (ch) (CHO-K1)	2.45 GHz, 5–200 W kg^{-1}, 2 h	No, micronucleus, no synergy with bleomycin
Falzone et al, 2010	Sperm (h)	90 MHz, 2 and 5.7 W kg^{-1}, 60 min, pulsed	No, DNA damage, apoptosis, ROS
Bourthoumieu et al, 2010	Amniotic cells (h)	900 MHz, 0.25 W kg^{-1}, 24 h, pulsed	No, chromosomal aberration
Belloni et al, 2005	Bacteria *(E. coli)*	900 MHz, 0.22 mW kg^{-1}, 3–24 h	Yes, anti-mutagenic effect
Chang et al, 2005	Bacteria *(E. coli)*	835 MHz, 4 W kg^{-1}, 48 h	No, Ames assay (test of carcinogenic potential)
Koyama et al, 2007	Bacteria *(Salmonella typhimurium) (E. coli)*, ovary cells (ch) (CHO-K1)	2.45 GHz, 5–200 W kg^{-1}, 30 min or 2 h	No, mutation at less than 50 W kg^{-1}

(h) = human, (m) = mouse, (r) = rat, (ch) = Chinese hamster
HL60 – human acute myeloid leukaemia cells, v79 – Chinese hamster fibroblast cells
BBB – blood-brain barrier, CW – continuous wave

TABLE 3.2 Possible carcinogenic effects

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Capri et al, 2004b	Lymphocytes (h)	900 MHz, 70 mW kg^{-1}, 1 h/day, 2 or 3 days	No, proliferation
Tai-Qin et al, 2008	Lymphocytes (h) (jurkat cells)	1763 MHz, 2–10 W kg^{-1}, 1–24 h	No, proliferation, comet
Lai et al, 2008	Leukaemia cells (HL60)	41.32 GHz, SAR?, 60 min	Yes, decreased proliferation, gene expression
Del Vecchio et al, 2009b	Cholinergic (SN56 cells), cortical neurons (r)	900 MHz, 1 W kg^{-1} up to 144 h	No, proliferation or viability Yes, synergistic oxidative damage SN56 only
Merola et al, 2006	Neuroblastoma	900 MHz, 24–72 h, 1 W kg^{-1}, pulsed	No, proliferation, apoptosis, differentiation
Höytö et al, 2008a	Neuroblastoma (h), fibroblasts (m)	872 MHz, 5 W kg^{-1}, 1 or 24 h, CW, pulsed	No, proliferation, apoptosis, ROS, Yes, +menadione, +butyl hydroperoxide
Buttiglione et al, 2007	Neuroblastoma (h)	900 MHz, 1 W kg^{-1}, 5 min – 24 h, pulsed	Yes, decreased proliferation
Miyakoshi et al, 2005	Glioma (h) (MO54 cells)	1950 MHz, 1–10 W kg^{-1}, 1–2 h	No, proliferation, heat shock proteins
Takashima et al, 2006	Glioma (h) (MO54 cells), ovary cells (ch) (CHO-K1)	2.45 GHz, 0.05–1500 W kg^{-1}, 2 h, 1 s on/1 s off, CW	No, proliferation No, non-thermal effects up to 100 W kg^{-1}
Sekijima et al, 2010	Glioma (h) (A172 cells), neuroglioma (H4 cells), fibroblasts (IMR-90 cells)	2 GHz, 80, 250, or 800 mW kg^{-1}, up to 96 h, CW	No, proliferation, gene expression
Pavicic et al, 2006	Fibroblasts (ch) (v79)	864 MHz, 0.08 W kg^{-1}, 1–3 h	Yes, decreased proliferation
Pavicic and Trosic, 2008a	Fibroblasts (ch) (v79)	864 and 935 MHz, 0.08–0.12 W kg^{-1}, 1–3 h	Yes, decreased proliferation
Trosic and Pavicic, 2009	Fibroblasts (ch) (v79)	935 MHz, 0.12 W kg^{-1}, 1–3 h	Yes, decreased proliferation
Pavicic and Trosic, 2006	Fibroblasts (ch) (v79)	864 MHz, 0.08 W kg^{-1}, 1–3 h	Yes, decreased proliferation
Pavicic and Trosic, 2008b	Fibroblasts (ch) (v79)	935 MHz, 0.12 W kg^{-1}, 1–3 h, CW	Yes, decreased proliferation after 3 h exposure

TABLE 3.2 *Continued*

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Duranti et al, 2005	Keratinocytes (h)	900 MHz, 0.04–0.08 W kg^{-1}, 18 h	Yes, decreased proliferation
Beneduci, 2009	Melanoma cells (h) RPMI 7932	42.20 and 53.57 GHz, 1 mW cm^{-2}, 1 h/4 days	No, cell proliferation and cell cycle
Beneduci et al, 2005	Melanoma cells (h)	50–80 GHz, <1 μW, 3 h/day, 7 days	Yes, antiproliferation effect on tumour cells
Tkalec et al, 2005	Duckweed	400–1900 MHz, 23 V m^{-1}, 2 h	Yes, 900 MHz decreased proliferation
Aksoy et al, 2005	Parasitic amoeba	900 MHz, No SAR, 24 h, 60 s/h, pulsed	Yes, decreased proliferation
Yu et al, 2002	Bacteria *(E. coli)*	42 GHz, 2.6 and 32 mW cm^{-2}, 40 min	No, proliferation
Cohen et al, 2010	Bacteria *(E. coli)*	99 GHz, 0.2 mW cm^{-2}, 1 or 19 h, CW	Yes, slight proliferation increase but no affect on metabolic activity Conclude effect has no biological meaning
Lee et al, 2008	Fibroblasts (m) (NIH3T3)	849 MHz, 2–10 W kg^{-1}, 1 min/day, 3 days	No, cell cycle
Capri et al, 2004a	Lymphocytes (h) young and old donors	1800 MHz, 1.4–2 W kg^{-1}, 44 h, 10 min on/20 min off	No, apoptosis or HSP
Palumbo et al, 2008	Lymphocytes (h) (jurkat cells)	900 MHz,1.35 W kg^{-1}, 1 h	Yes, apoptosis
Lee et al, 2005	Leukaemia cells (HL60)	2.45GHz, 10 W kg^{-1}, 2 h, pulsed	Yes, apoptosis-associated gene expression
Lantow et al, 2006c	Monocytes (h) (monomac cells)	1800 MHz, 2 W kg^{-1}, 12 h	No, apoptosis, DNA synthesis
Chauhan et al, 2007a	HL60, TK6, monomac	1900 MHz, 1–10 W kg^{-1}, 6 h, 5 min on/10 min off	No, apoptosis
Marinelli et al, 2004	Lymphoblastoid	900 MHz, 3.5 mW kg^{-1}, 2–48 h	Yes, apoptosis
Joubert et al, 2007	Neurons (r)	900 MHz, 0.25 W kg^{-1}, 24 h, pulsed	No, apoptosis
Joubert et al, 2008	Neurons (r)	900 MHz, 2 W kg^{-1}, 24 h, CW	Yes, apoptosis
Zhao T et al, 2007	Neurons (m)	1900 MHz, no SAR given, 2 h, pulsed	Yes, apoptosis-associated gene expression

TABLE 3.2 *Continued*

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Joubert et al, 2006	Neuroblastoma (h)	900 MHz, 2 W kg^{-1}, 24 h, CW, pulsed	No, apoptosis
Moquet et al, 2008	Neuroblastoma (m)	935 MHz, 2 W kg^{-1}, 24 h	No, apoptosis
Hirose et al, 2006	Fibroblasts (h) (IMR-90), glioma (h) (A172 cells)	2.14 GHz, <800 mW kg^{-1}, 24, 28 or 48 h	No, apoptosis
Cao et al, 2009	Glioma (h) (5HG44 cells)	900 MHz, 2–6 mW cm^{-2}, 2 h/day, 3 days	No, apoptosis Yes, synergy with gamma rays
Nikolova et al, 2005	Stem cells (m)	1710 MHz, 1.5 W kg^{-1}, 5 min on/25 min off, after 6 h but not 48 h	Yes, apoptosis-related genes
Caraglia et al, 2005	Epidermoid cancer cells (h)	1950 MHz, 3.6 mW kg^{-1}, 1–48 h	Yes, apoptosis
Markkanen et al, 2004	Yeast	900 MHz, 0.4–3 W kg^{-1}, 1 h	No, apoptosis Yes, synergy with UVR
Cranfield et al, 2003a	Bacteria (magnetotactic)	900 MHz, SAR?, 16 min, pulsed	Yes, cell death, but not due to RF (see Cranfield et al, 2003b)
Cranfield et al, 2003b	Bacteria (magnetotactic)	800 MHz, 2 W kg^{-1}, 30 min	No, cell death, suggest 2 Hz effect
Sharma et al, 2009	Mung bean	900 MHz, 8.55 μW cm^{-2}, 0.5, 1, 2 and 4 h	Yes, germination decreased, ROS increased
Sharma et al, 2010	Mung bean	900 MHz, 8.55 μW cm^{-2}, 0.5, 1, 2 and 4 h	Yes, 4 h impaired early growth of seedlings
Billaudel et al, 2009a	Neuroblastoma (h) (SH-SY5Y cells)	835/1800 MHz, 1–2.5 W kg^{-1}, 8–24 h, pulsed	No, ODC activity
Desta et al, 2003	Fibroblasts (m) (L929 cells)	835 MHz, <1–15 W kg^{-1}, 8 h	No, ODC activity
Höytö et al, 2006	Fibroblasts (m) (L929 cells)	900 MHz, 0.2–0.4 W kg^{-1}, 2, 8 or 24 h, pulsed	No, ODC (ODC temperature sensitive, 0.8°C increase causes ODC decrease)
Höytö o et al, 2007a	Fibroblasts (m) (L929 cells), neuroblastoma (SH-SY5Y cells), primary astrocytes	872 MHz, 1.5–6.0 W kg^{-1}, 2, 8 or 24 h, CW, pulsed	Yes, ODC activity only decreased in primary cells not cell lines
Höytö et al, 2007b	Fibroblasts (m) (L929 cells)	835/872 MHz, 2.5 or 6.0 W kg^{-1}, 2, 8 or 24 h	No, ODC, inconsistency of findings

TABLE 3.2 *Continued*

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Höytö et al, 2008a	Fibroblasts (m) (L929 cells), neuroblastoma (SH-SY5Y cells)	872 MHz, 5 W kg^{-1}, 1 or 24 h	No, ODC, but synergy with stressors
Höytö et al, 2008b	Fibroblasts (m) (L929 cells)	872 MHz, 5 W kg^{-1}, 1 and 24 h, CW, pulsed	No, caspase, ODC activity, proliferation
Billaudel et al, 2009b	Fibroblasts (m) (L929 cells)	900 MHz, 1800 MHz, 0.5–6 W kg^{-1}, 2–24 h, pulsed	No, ODC activity
Zeni et al, 2007	Fibroblasts (m) (L929 cells)	900 MHz, 0.3 and 1 W kg^{-1}, 10 or 30 min, CW, pulsed	No, ROS, ± mutagen (3-chloro-4-dichloromethyl-5-hydroxy-2-5H furanone)
Brescia et al, 2009	Lymphoblastoid cell (h)	1950 MHz, 0.5 and 2.0 W kg^{-1}, short 5–60 min or long 24 h	No, ROS with or without ferrous ions No, synergy
Zmyslony et al, 2004	Lymphocyte (r)	930 MHz, 1.5 W kg^{-1}, 5 or 15 min, CW	No, ROS Yes with iron ion stimulation
Xu et al, 2010	Neurons (r)	1800 MHz, 2 W kg^{-1}, 24 h, 5 min on/10 min off	Yes, mitochondrial DNA oxidative damage, ROS increased
Crouzier et al, 2009	Yeast	9.71 GHz, 0.5–16 W kg^{-1}, 20 min, pulsed	Yes, free radicals increased

(h) = human, (m) = mouse, (r) = rat, (ch) = Chinese hamster
HL60 – human acute myeloid leukaemia cells, TK6 – lymphoblastoma cells, v79 – Chinese hamster fibroblast cells, L929 – mouse fibroblasts
CW – continuous wave

3.2.3 Apoptosis

Apoptosis is cell death by a controlled sequence of cellular events that eliminates the cell without releasing harmful substances into its local environment. Apoptosis plays a normal and vital role in maintaining health by eliminating old, DNA damaged, and unhealthy cells.

Prior to 2004 there were only a few studies on RF fields that specifically measured apoptosis and in the previous AGNIR review the single study of apoptosis was included in the section on proliferation (AGNIR, 2003).

Apoptosis, along with proliferation, can be considered a major measurable endpoint that results from biological changes in the *in vitro* cell system (Table 3.2). There are a variety of methods used to assess apoptosis but one distinction that may be important is whether the pathway that leads a cell to apoptosis uses the caspase enzymes (many of the studies use caspase as a measure of apoptosis) or whether the pathway is independent of caspase, in which case a measure of caspase would not observe the change.

TABLE 3.3 Gene expression

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Capri et al, 2006	Lymphocytes (h) 10 young, 8 elderly	1800 MHz, 2 W kg^{-1}, 44 h, 10 min on/20 min off, pulsed	Yes, cd95 expression down regulated in old stimulated cells
Tuschl et al, 2006	Monocytes (h)	1950 MHz, 1 W kg^{-1}, 8 h, 5 min on/ 10 min off	No, immune, gene expression
Gerner et al, 2010	Lymphoblastoid cells (h), fibroblasts (h), mononuclear cells (h)	1800 MHz, 2 W kg^{-1}, 8 h, 5 min on/10 min off	Yes, increased protein synthesis
Zhao R et al, 2007	Neurons (r)	1800 MHz, 2 W kg^{-1}, 24 h, 5 min on/10 min off, pulsed	Yes, gene expression: 24 genes increase and 10 genes decrease
Thorlin et al, 2006	Astroglial, microglial cells	900 MHz, 2.8–25 W kg^{-1}, pulsed, or 27 and 54 W kg^{-1}, 4–24 h	No, cytokines
Hirose et al, 2010	Microglial cells (r)	1950 MHz, 0.2. 0.8 and 2.0 W kg^{-1}, 2 h	No, cell activation or expression of cytokines
Nicolaz et al, 2009	Glial (U-251 MG cells)	60 GHz, 2.64–3.3 W kg^{-1}, 24 h	No, expression of two endogenous endoplasmic reticulum stress biomarkers
Whitehead et al, 2006a	Fibroblast (m) (C3H10T½ cells)	835/847 MHz, 5 W kg^{-1}, 8 h, FDMA, CDMA	No, gene expression
Whitehead et al, 2006b	Fibroblast (m) (C3H10T½ cells)	835/847 MHz, 5 W kg^{-1}, 8 h, FDMA, CDMA	No, gene expression
Whitehead et al, 2005	Fibroblast (m) (C3H10T½ cells)	835/847 MHz, 5.2 or 10 W kg^{-1}, 4 days	No, Fos mRNA (did not confirm Goswami, 1999)
Im et al, 2010b	Fibroblast (h) (WI-38 cells)	1763 MHz, 60 W kg^{-1}, 24 h	No, gene expression
Lee et al, 2007	Auditory cells (m) (HEI-OC1)	1763 MHz, 20 W kg^{-1}, 24 h	Yes, gene expression
Zeng et al, 2006	Breast cancer (MCF7 cells)	1800 MHz, 2 or 3.5 W kg^{-1}, 1–24 h, 5 min on/10 min off, pulsed	No, gene and protein expression
Dawe et al, 2009	Nematode *(C. elegans)*	1.0 GHz, 0.9–3 mW kg^{-1}, 1.5, 2.5 or 6 h	No, gene expression

(h) = human, (m) = mouse, (r) = rat

TABLE 3.4 Stress effects, expression of heat shock protein

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Lee et al, 2006	Lymphocytes (h)	1783 MHz, 2 or 20 W kg^{-1}, 30 min or 1 h	No, HSP90, HSP70, HSP27 No, synergy with TPA
Lantow et al, 2006a	Lymphocytes (h), monocytes	1800 MHz, 2 W kg^{-1}, 30–45 min, 5 min on/off, CW, pulsed	No, HSP70, ROS
Cherenkov et al, 2009	Lymphocytes (m)	8.15–18.0 GHz, 1 μW cm^{-2}, 1 h	Yes, stimulation of stress signal pathway
Chauhan et al, 2006a	Lymphoblastoma (h)	1900 MHz, 1 and10 W kg^{-1}, 6 h, 5 min on/10 min off	No, HSP gene expression
Chauhan et al, 2006b	Leukaemia cells (HL60), monocyte (h) (monomac cells)	1900 MHz, 1 and 10 W kg^{-1}	No, stress, HSP70, HSP27
Hook et al, 2004	Macrophage (m) (J774.16)	835/847 MHz, 0.8 W kg^{-1}, 22 h, CW	No, oxidative stress, in stimulated or unstimulated cells
Simko et al, 2006	Monocyte (h) (monomac cells)	1800 MHz, 2 W kg^{-1}, 1 h, CW, pulsed	No, HSP70, stress, with or without ultrafine particles
Lantow et al, 2006b	Monocyte (h) (monomac cells) leukaemia (K562 cells)	1800 MHz, 0.5–2 W kg^{-1}, 45 min or 1 h, CW, pulsed	No, HSP70 expression or free radicals
Gurisik et al, 2006	Monocyte (h) (U937) neuroblastoma (h) (SK-N-SH)	900 MHz, 0.2 W kg^{-1}, 1 or 2 h, pulsed	No, HSP genes and protein
Chauhan et al, 2007b	Monocyte (h) (monomac cells), glioma (h) (U87MG)	1900 MHz, 0.1–10 W kg^{-1}, 5 min on/10 min off, 24 h, pulsed	No, HSP genes
Im et al, 2010a	Fibroblast (h) (WI-38 cells)	1763 MHz, 60 W kg^{-1}, 24 h	No, 3 heat shock proteins (HSP) and 7 stress-related genes
Qutob et al, 2006	Glioma (U87MG)	1900 MHz, 0.1–10 W kg^{-1}, 4 h, pulsed	No, HSP genes
Hirose et al, 2007	Glioma (h) fibroblasts	2.14 GHz, 80–800 mW kg^{-1}, 2–48 h	No, HSP phosphorylation, HSP27
Wang et al, 2006	Glioma (h) (A172 cells)	2.45 GHz, 5–200 W kg^{-1}, 1–3 h	No, HSP70, HSP27, no non-thermal effect
Zhadobov et al, 2007	Glioma (h) (U251)	60 GHz, 0.54 or 5.4 mW cm^{-2}, 1–33 h	No, stress, mRNA, protein expression

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Laszlo et al, 2005	Carcinoma (h) (HeLa S3) fibroblasts (hamster ovary HA-1) (C3H10T½) (m)	836/848 MHz, 0.6 or 5 W kg^{-1}, 5 min – 24 h	No, stress response, HSFactor
Sanchez et al, 2007	Keratinocytes (h) fibroblasts (h)	1800 MHz, 2 W kg^{-1}, 48 h	No, stress, HSP70, HSC70, HSP27
Sanchez et al, 2006	Keratinocytes (h)	900 MHz, 2 W kg^{-1}, 48 h	Yes, HSP70 slight increase
Szabo et al, 2003	Keratinocytes (h)	61.2 GHz, 770 W kg^{-1}, 42.25 GHz, 37 W kg^{-1}, 30 or 60 min, CW	No, HSP70, gap junction
Czyz et al, 2004	Embryonic stem cells	1710 MHz, 0.4–2 W kg^{-1}, 6–72 h, 5 min on/30 min off, pulsed	Yes, mRNA HSP in p53 (tumour suppressor) deficient cells
Franzellitti et al, 2008	Trophoblast (h)	1800 MHz, 2 W kg^{-1}, 4–24 h, 5 min on/10 min off, CW, pulsed	Yes, only HSP70c No protein detected

(h) = human, (m) = mouse, (r) = rat
HL60 – human acute myeloid leukaemia cells
CW – continuous wave

calcium efflux and their significance were disputed. The design and interpretation of the early studies were not ideal and they were predominantly carried out using non-living tissue. By 2003 a number of generally better designed studies had found no increase of calcium efflux from tissues as a result of RF field exposure under a variety of conditions and modulations (AGNIR, 2003).

Only four further studies have been added to the literature (see Table 3.5). All of them included the effects of RF field exposure on neurons as well as investigations into other cell types. At 380 MHz (TETRA frequencies) no effect was found over a wide range of exposures (Green et al, 2005). The other three studies used mobile phone frequencies and found contradictory results. No effect was found using 900 MHz at an SAR of up to 2 W kg^{-1} (Platano et al, 2007; O'Connor et al, 2010), whereas 800 MHz at a range of SAR values caused increased calcium signalling (Rao et al, 2008); interestingly the effect was frequency dependent but not SAR dependent. The continued lack of demonstrable effects at TETRA frequencies is reassuring in that concern was expressed about this frequency and its modulation close to 16 Hz. However, the finding that calcium signalling was increased at 800 MHz means that there is still controversy and that no definite conclusions can be made. If the phenomenon is biologically significant, concomitant changes would be expected in the functions of nervous tissues that depend on the movement of calcium ions, but none has been unambiguously shown to occur.

TABLE 3.5 Intracellular signalling

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Platano et al, 2007	Neurons (r)	900 MHz, 2 W kg^{-1}, 90 s every 2–3 min, repeated 3x, pulsed, CW	No, calcium channels
Rao et al, 2008	Neuronal cells (m)	700–1100 MHz, 0.5 W kg^{-1}, 800 MHz, 0.5–5 W kg^{-1}, 1 h	Yes, calcium spikes increase, frequency (800 MHz) not SAR dependent
Green et al, 2005	Myocytes (r), neurons (r)	380 MHz, 5–400 mW kg^{-1}, 11–40 min, CW	No, calcium signalling
O'Connor et al, 2010	Endothelial cells (h), neuroblastoma (PC-12 cells), hippocampal neurons	900 MHz, 0.012–2 W kg^{-1}, 30 min, pulsed, CW	No, calcium signalling

(h) = human, (m) = mouse, (r) = rat
CW – continuous wave

3.3.3 Membrane effects

The cell membrane is a lipid bilayer that plays an important role in cellular function, from maintaining the correct internal cell environment to mediating and interpreting external signals. However, cells can also bind together to form a membrane such as the blood-brain barrier.

The view of the IEGMP (2000) was that there was evidence that exposure to RF fields can affect membrane proteins and the movement of ions across membranes. However, some of the effects only occur at temperatures outside the normal physiological range. The previous AGNIR review (2003) had little more to add; it found the results from the *in vitro* blood-brain barrier models interesting but in need of *in vivo* confirmation.

Several more recent studies have investigated the possible effect on membranes of exposure to RF fields (see Table 3.6). These studies can be divided into those looking at effects where multiple cells unite to form a membrane such as the blood-brain barrier and those on the individual cell's membrane.

The blood-brain barrier restricts the movement of some substances from the blood into the brain and is achieved by tight junctions between endothelial cells that line the capillaries of the central nervous system. The possibility for substances that do not normally cross the blood-brain barrier being able to do so due to the influence of RF field exposure has raised some concern. Studies that address this question directly are usually *in vivo* investigations; however, there are some *in vitro* models of the blood-brain barrier and these have been investigated with reference to RF field exposure to look at possible changes in permeability of the membrane. Two studies found no effect on permeability. The study by Franke et al (2005a) was a repeat of their earlier work at 1800 MHz but with an improved model of the blood-brain

TABLE 3.6 Membrane effects

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Franke et al, 2005a	Astrocyte/ endothelial co-culture (BBB model)	1800 MHz, 0.03–0.46 W kg^{-1}, 5 days, pulsed	No, permeation in improved model, could not replicate own work
Franke et al, 2005b	Endothelial cells (BBB model)	966 MHz,1.8 W kg^{-1}, 24–84 h	No, effect on permeability
Kuo and Kuo, 2008	Endothelial cells (BBB model)	915 MHz, 5 mW, 90 min, CW	Yes, increased permeability
Chen et al, 2008	Keratinocytes (h) (HaCaT)	30.16 GHz, 1 or 3.5 mW cm^{-2}, 1 h	No, gap junction Yes, TPA stimulated
Stankiewicz et al, 2006	Lymphocytes (h)	900 MHz, 0.024 W kg^{-1}, 15 min/day, 3 days, pulsed	Yes, response to mitogens (PHA con A) increased
Mahrour et al, 2005	Melanoma (m) CHL fibroblasts, carcinoma A253	900 MHz, 1.3–2.6 W kg^{-1}, >10 min, CW, pulsed	Yes, increased endocytosis, electric field effect
Moisescu et al, 2009	Melanoma (m) (B16F10)	900 MHz, 3.2 W kg^{-1}, 20 min, pulsed	Yes, endocytosis rate increased
Aly et al, 2008	Neutrophils (h)	900 MHz, 0.4 V m^{-1}, 15 min	Yes, motion (chemotaxis) increased
Cervellati et al, 2009	Trophoblast (HTR-8/SVneo cells)	1817 MHz, 2 W kg^{-1}, 1 h	Yes, expression of connexins (membrane proteins) increased
Erogul et al, 2006	Sperm (h)	900 MHz, 2 W kg^{-1}, 5 min, pulsed	Yes, motility decreased
Falzone et al, 2008	Sperm (h)	900 M Hz, 2–5.7 W kg^{-1}, 1 h	Yes, motility decreased at higher SAR
De Iuliis et al, 2009	Sperm (h)	1.8 GHz, 1–27.5 W kg^{-1}, 16 h	Yes, motility and vitality reduced, mitochondrial ROS increased, DNA damage
Agarwal et al, 2009	Sperm (h)	850 MHz, 1.46 W kg^{-1}, 1 h, pulsed	Yes, sperm motility and viability decreased, ROS increased
Pakhomov et al, 2003	Hippocampus slices (r)	9.3 GHz, 0.25–360 kW kg^{-1}, duration?, CW, pulsed	No, synaptic transmission between neurons, thermal effect only
Xu et al, 2006	Hippocampal neurons (r)	1800 MHz, 2.4 W kg^{-1}	Yes, synaptic activity decreased
Szabo et al, 2006	Keratinocytes (h) (HaCaT) (m), melanoma (B16F10)	2.25 GHz, 1.23 W cm^{-2}, 30 min	Yes, membrane, externalisation of phosphatidylserine

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Zhadobov et al, 2006	Phospholipid membrane (model)	60 GHz, <0.9 W cm^{-2}, 1–7 h, CW	Yes, lateral pressure increased
Mohammadzadeh et al, 2009	Artificial lipid bilayer porin channel	925 MHz, 0.03 W cm^{-2}, duration?	Yes, membrane dynamics and conformation of the channel, millisecond effect, possibly due to heating
Gaber Mohamed et al, 2005	Vesicle bilayer	900 MHz, 12 W kg^{-1}, 5 h	Yes, increased damage to vesicles Conclude effect due to heating
Del Vecchio et al, 2009a	Cholinergic cells (m)	900 MHz, 1 W kg^{-1}, 1–6 day	Yes, neurite number decreased but not length
Crouzier et al, 2009	Yeast *(Saccharomyces cerevisiae)*	9.71 GHz, 0.5–16 W kg^{-1}, 20 min	Yes, decreased membrane fluidity consistent with lipid peroxidation, suggest an increase of the free radical production

(h) = human, (m) = mouse, (r) = rat
CW – continuous wave

In general, most studies report finding effects on cell membranes when exposures are made at mobile phone frequencies. However, the effects reported are varied and, although the majority find effects, neither is this unanimous nor does it necessarily provide supporting evidence of a consistent effect. The variety of cellular systems and exposures makes comparisons of the effects on the cell membrane problematic and without independent replication it is difficult to assess the robustness or even validity of the findings.

3.3.4 Direct effect on proteins

Enzymes are proteins that catalyse chemical reactions; each enzyme is specific to a particular reaction and hence there are hundreds of different types of enzymes in the body. They play a vital role in function both within cells and in the body fluids, their activity being regulated by various local factors. Other types of protein also exist and play important roles in structure and function.

There were only a few studies prior to the earlier AGNIR report (AGNIR, 2003). All those reviewed in that report used frequencies of 2.45 GHz or higher; all found effects either showing stimulation or inhibition of enzyme activity. The studies were too few and diverse to be able to draw any conclusions.

Since 2003 there have been a few more enzyme studies, but additionally there have been investigations into effects on other types of proteins (see Table 3.7). Three enzyme studies used 2.45 GHz exposures with SAR values close to 5 W kg^{-1} and found reductions in activity in three different enzymes (Ramundo-Orlando et al, 2004; Vukova et al, 2005; George et al, 2008). A study using 1.1 GHz at 90 or 192 mW (no SAR value given) to investigate epithelial cell damage in the lens of the eye found increased enzyme activity leading to increased lens damage (Bormusov et al, 2008). Also 875 MHz exposure at less

TABLE 3.7 Direct effect on proteins

Study	Cellular system	Exposure conditions	Effect of exposure and measure
Friedman et al, 2007	Epithelial (h) (HeLa cells)	875 MHz, 0.005–0.3 mW cm^{-2}, 2–30 min	Yes, kinase activity, signal transduction pathways
Bormusov et al, 2008	Epithelium (eye lens)	1.1 GHz, 2.22 mW, 90 or 192 cycles of 50 min	Yes, enzyme activity increased, lens damage
Mousavy et al, 2009	Haemoglobin	910/940 MHz,15.7 W m^{-2}, 1 or 2 h	Yes, tertiary structure of haemoglobin, oxygen affinity
Mancinelli et al, 2004	Myoglobin refolding in solution	1950 MHz, 51 mW kg^{-1}, 3 h, CW	Yes, refolding in acid conditions
Bismuto et al, 2003	Myoglobin refolding in solution	1950 MHz 51 mW kg^{-1}, 2.5 h, CW	No, protein structure, normal pH conditions
Belyaev et al, 2005	Chromatin in lymphocytes (h)	915 MHz, 37 mW kg^{-1}, 2 h, pulsed	Yes, increased conformational change
Cespedes and Ueno, 2009	Ferritin protein	1 MHz, 30 μT, up to 9 h	Yes, rates of iron chelation with ferrozine are reduced
Cespedes et al, 2010	Ferritin protein	1 MHz, 30 μT, 2 h	Yes, proteins have a reduced iron intake rate
Schrader et al, 2008	Human-hamster hybrid cell	835 MHz, 60 mW kg^{-1}, 0.5–2 h, CW	Yes, spindle disturbance
Sukhotina et al, 2006	Pineal gland (hamster)	1800 MHz, 0.008–2.7 W kg^{-1}, 7 h, CW, pulsed	Yes, melatonin release increased above 800 mW kg^{-1}
Sandu et al, 2005	Black locust seedlings	400 MHz, 2W, 1–8 h, 3 weeks	Yes, chlorophyll decreased except at 2 h which increased
Ramundo-Orlando et al, 2004	Enzyme activity (ascorbate oxidase)	2.45 GHz, 1.4–5.6 W kg^{-1}, 3 min	Yes, at 5.6W kg^{-1} only, enzyme activity reduced
Vukova et al, 2005	Enzyme activity (acetyl-cholinesterase)	2.45 GHz, 4.92 W kg^{-1}, 30 min	Yes, activity decreased, conformational change
George et al, 2008	Protein (citrate synthase)	2.45GHz, 4.85 W kg^{-1}, 10–20 s	Yes, protein unfolding, claim non-thermal
Weissenborn et al, 2005	Globular protein	8 GHz, 0.5–3 W,10 min and 4 h	Yes, structural alteration
Copty et al, 2006	Green fluorescent protein	8.35 GHz, <4000 W kg^{-1}, duration?	Yes, fluorescence decrease more than thermal effect

(h) = human
CW – continuous wave

than 0.3 mW cm^{-2} was shown to increase enzyme activity associated with signalling pathways inside epithelial cells (Friedman et al, 2007). Some of these changes in enzyme activity, particularly reductions in activity, have been associated with changes in the structure of the enzyme (Vukova et al, 2005; George et al, 2008). Such structural changes have also been reported in other proteins. The tertiary structure of haemoglobin, and hence its ability to bind oxygen, was affected by exposure to 900 MHz at 15.7 W m^{-2} (Mousavy et al, 2009). Ferritin, another protein that binds iron, was shown to have reduced rates of iron binding when exposed to 1 MHz at 30 μT (Cespedes and Ueno, 2009; Cespedes et al, 2010). Myoglobin was affected at 1950 MHz at 51 mW kg^{-1} under acid conditions (Mancinelli et al, 2004), but it was unaffected under more neutral pH conditions (Bismuto et al, 2003). However, another globular protein, lysozyme, showed little if any non-thermal change in response to 8 GHz at 0.5–3 W exposure (Weissenborn et al, 2005), but green fluorescent protein exposed to a similar frequency (8.35 GHz) had effects greater than heating alone (Copty et al, 2006). Conformational changes may not be restricted to protein only, chromatin (a combination of DNA and protein) was reported to undergo similar conformational changes to those caused by heat when exposed to 915 MHz at 37 mW kg^{-1} for 2 hours (Belyaev et al, 2005). Other studies that possibly show direct effects of RF field exposure on proteins are the spindle disturbance reported in a human-hamster hybrid cell that occurs after exposure to 835 MHz at 60 mW kg^{-1} (Schrader et al, 2008); the decrease in chlorophyll in black locust seedlings after exposure to 400 MHz at 2 W (Sandu et al, 2005); and the increased release of melatonin from isolated pineal glands after exposure to 1800 MHz above 0.8 W kg^{-1} (Sukhotina et al, 2006).

In general, most of the studies that have investigated changes in protein function or structure due to exposure to RF fields have found effects. However, at the present time the effects have not been demonstrated to be robust by independent replication; so although the concept of a direct effect of RF field exposure on protein structure is interesting, further research is needed to establish if this is a real phenomenon.

3.4 Summary

Many more studies have been added to the scientific literature since 2003, with more studies using similar cell types and exposure conditions, thus potentially making comparisons and conclusions easier. However, the results of the additional findings still remain divergent with no obvious reason as to why some researchers find effects and others do not. There is still a lack of independent replication of results, and where replications have been undertaken they do not support the original findings. This continued lack of robust evidence makes the possibility of an effect of RF fields on cells more unlikely.

In terms of direct genotoxic effects of exposure to RF fields, the evidence for an effect is not convincing and still remains weak. There was some evidence of synergistic effects of RF fields with known carcinogens; however, not all studies that investigated this possibility found such effects, nor were the reported effects supported by independent replication, thus making a decision as to whether there is a real effect uncertain.

Of the effects that could possibly lead to carcinogenesis there was no evidence of cell transformation or an increased rate of cell proliferation in response to exposure to RF fields. The results of the studies on

cell proliferation rate were mixed, some finding a decreased rate and others finding no change. A decrease in rate is reassuring in that one concern was that exposure to RF fields could stimulate tumour cell growth: this appears not to be the case. Apoptosis (programmed cell death) and production of reactive oxygen species (ROS) were increased in some studies, but not in others using similar conditions. Previously, concerns were raised that the activity of the enzyme ornithine decarboxylase (ODC) was increased by RF field exposure, but three independent research groups have found no such effect on this enzyme's activity.

An area of interest in the last AGNIR report on RF fields (2003) was the possible involvement of stress proteins in the cellular response to RF field exposure; much of the work was devoted to investigating heat shock proteins, a group of proteins that mediate general stress effects, not just those caused by heat. Most of the newer studies have found no effect of RF field exposure on heat shock proteins. There were only a few new studies on calcium flux in cells and these mainly found no effect of exposure to RF fields. The general 'no effect' nature of the more recent findings supports the view that there is no RF modulation of calcium ion concentrations in cells. Results from studies of gene expression in cells were mixed, whereas those from studies on cell membranes and direct effects on proteins mostly found effects of RF field exposure. However, no conclusions can be made as there are no common patterns of exposure conditions or types of effect caused by exposure.

In general, there is no coherent pattern of exposure conditions or *in vitro* cell system that consistently shows effects of exposure to RF fields below international guideline levels. The reported studies are still mostly diverse in terms of exposure and biological system tested; furthermore the reported effects lack independent verification. Even in cases where there are several studies using similar cell types, as in the case of lymphocytes, the results for the effect of RF field exposure are conflicting.

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TABLE 4.1 Animal studies investigating effects on cellular physiology, injury and apoptosis, mainly in the brain and nervous tissue

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Finnie, 2005	*c-fos* expression in C57BL/6NTac mouse brain using immunohistochemistry (IHC)	900 MHz GSM, 1 h at 4 W kg^{-1}, animals restrained	No significant effects in cortex	Effects of immobilisation stress observed
Finnie et al, 2007	*c-fos* expression in *Eμ-Pim 1* mouse brain using IHC	900 MHz GSM, 1 h/day, 5 days/week for 104 days at 4 W kg^{-1}, animals restrained	No significant effects in cortex or hippocampus, effects of restraint stress seen	Model predisposed to spontaneous lymphoma development, tumour-free animals only used
Finnie et al, 2010	Ionised calcium binding adaptor molecule (Iba1) expression in mouse brain using IHC	900 MHz GSM, 1 h or 1 h/day, 5 days/week for 104 days at 4 W kg^{-1}, animals restrained	No significant effects in cingulate cortex or hippocampus	Stab wound produced substantial effects Mouse strain not specified
Finnie et al, 2006a	*c-fos* expression in fetal BALB/c mouse brain using IHC on gestation day 19	900 MHz GSM, 1 h/day from day 1–19 of gestation at 4 W kg^{-1}, animals restrained	No significant effects in pyriform cortex or basal ganglia	–
Finnie et al, 2009	HSP25, 32, 70 expression in fetal BALB/c mouse brain using IHC on gestation day 19	900 MHz GSM, 1 h/day from day 1–19 of gestation at 4 W kg^{-1}, animals restrained	No effects	HSPs induced in neonates by hyperthermic shock
Paparini et al, 2008	Gene expression in BALB/cJ mouse brain using microarrays	1800 MHz GSM, 1 h at 1.1 W kg^{-1}, 0.2 W kg^{-1} in brain, animals restrained	No significant effects	With reduced stringency, 75 genes up-regulated or down-regulated <0.67 and >1.5-fold, none confirmed by RT-PCR
Kim et al, 2008	Proliferating cell nuclear antigen (PCNA), Terminal deoxynucleotidyl transferase dUTP Nick End Labeling (TUNEL), NeuN (Neuronal Nuclei), glial fibrillary acidic protein (GFAP) in C57BL/6N mouse brain, by IHC	849 or 1763 MHz CDMA, 1 h/day, 5 days/week for 6 or 12 months at 7.8 W kg^{-1} in brain, head-only exposure, animals restrained	No effects on cell proliferation, apoptosis, distributions of neurons and reactive astroglial cells No effect on body weight	Animals 8 weeks old at start of exposure

Study	Model used	Exposure conditions	Results of exposure	Comments
Grafström et al, 2008	GFAP expression, lipofuscin aggregation, Cresyl violet, Gallyas, Sudan Black B stains, in Fischer 344 rat brains 5–7 weeks after exposure	900 MHz GSM, 2 h/week for 55 weeks at 0.006 or 0.06 W kg^{-1}, animals confined in TEM cell	No significant effects on GFAP, dark neurons, cytoskeleton or neuronal changes	No voice modulation, SAR reduced over time due to animal growth, by x 0.3 at end
Anane et al, 2003	Acute experimental allergic encephalomyelitis induced in Lewis rats, scored for clinical signs	900 MHz GSM, 2h/day for 21 days at 1.5 or 6 W kg^{-1} in brain, head-only exposure, animals restrained	No significant effects, with or without habituation to restraint	Preliminary study
Poulletier de Gannes et al, 2009a	Cresyl violet and FluoroJade B, TUNEL in Fischer 344 rat brain, 14 and 50 days after exposure	900 MHz GSM, 2 h at 0.14 or 2 W kg^{-1} in brain, head-only exposure, animals restrained	No significant increase in apoptosis or dark neurons	Did not replicate Salford et al, 2003 Cold shock induced significant increase in degenerating neurons
Masuda et al, 2009	Cresyl violet, haematoxylin and eosin (H&E), neuronal morphology, in Fischer 344 rat brain, 14 and 50 days after exposure	915 MHz GSM, 2 h at 0.02, 0.2 or 2 W kg^{-1}, animals confined in TEM cell	No significant increase in dark neurons, no morphological changes	Did not replicate Salford et al, 2003 Cold shock and chemical injury induced significant increases in dark neurons
Kumlin et al, 2007	Cresyl violet, FluroJade B, Doublecortin, proliferating cell nuclear antigen (PCNA), phosphorylated cAMP response element-binding protein (pCREB), in young Wistar rat brain, using IHC	900 MHz GSM, 2h/day, 5 days/week for 5 weeks at 0.3 or 3 W kg^{-1}, animals freely moving	No significant effects on hippocampus and dentate gyrus	Examined in 35 μm sections
Lee et al, 2005	PCMA, H&E, TUNEL in *hsp*70.1-deficient mouse brain, using IHC	849 or 1763 MHz CMDA, 90 min/day (2 x 45 min with 15-min interval), 5 days/week for 4, 8 or 10 weeks at 0.4 W kg^{-1}, animals freely moving	No significant effects on apoptosis, or cell proliferation	–

TABLE 4.1 *Continued*

Study	Model used	Exposure conditions	Results of exposure	Comments
Belyaev et al, 2006	Gene expression in Fisher 344 rat cerebellum, using microarrays	915 MHz GSM, 2 h at 0.4 W kg^{-1}, animals confined in TEM cell	11 genes up-regulated 1.3–2.7-fold, one gene down-regulated 0.48 fold No change in hsp70 using Western blot	Genes encode diverse functions No effects on DNA damage
López-Martin et al, 2006, 2009	*c-fos* expression in Sprague-Dawley (SD) rat brain made seizure-prone with picrotoxin (2 mg kg^{-1})	900 MHz GSM or CW, 2 h at 0.03–0.05 or 0.27–0.42 W kg^{-1} in brain (GSM) or 0.26 W kg^{-1} in brain (CW), animals restrained	Picrotoxin alone increased c-fos, GSM plus picrotoxin significantly increased seizure activity and c-fos activity, particularly in the limbic system, smaller effects with CW	5 steel screws inserted into skull as electrodes to measure EEG
Mausset-Bonnefont et al, 2004	GFAP expression, in Wistar rat brain 3 days after exposure	900 MHz GSM, 15 min at 6 W kg^{-1} in brain, head-only exposure, animals restrained	Significant increase in GFAP, particularly in striatum	No significant changes in locomotory behaviour in open field
Brillaud et al, 2007	GFAP expression, in SD rat brain at 2, 3, 6 and 10 days after exposure	900 MHz GSM, 15 min at 6 W kg^{-1} in brain, head-only exposure, animals restrained	Significant increase in GFAP after 2 and 3 days in frontal cortex and caudate putamen	Transient effects only: no changes observed after 3 days
Ammari et al, 2008a	GFAP expression in SD rat brain 10 days after exposure, using IHC	900 MHz GSM, 45 min/day at 1.5 W kg^{-1} in brain or 15 min/day at 6 W kg^{-1} in brain, 5 days/week for 24 weeks, head-only exposure, animals restrained	Significant increase in prefrontal cortex, dentate gyrus, caudate putamen, lateral globus pallidus (but not cerebellar cortex) at higher SAR only	–
Ammari et al, 2010	GFAP expression in SD rat brain 3 and 10 days after exposure, using IHC	900 MHz GSM, 45 min/day at 1.5 W kg^{-1} in brain or 15 min/day at 6 W kg^{-1} in brain, 5 days/week for 8 weeks, head-only exposure, animals restrained	Significant increase in all areas at both SARs after 3 days, in prefrontal cortex and dentate gyrus at higher SAR, in lateral globus pallidus at both SARs after 10 days	Results variable between animals

Study	Model used	Exposure conditions	Results of exposure	Comments
Ammari et al, 2008b	Cytochrome c oxidase (CO) activity in SD rat brain, 7 days after exposure	900 MHz GSM, 45 min/day at 1.5 W kg^{-1} in brain or 15 min/day at 6 W kg^{-1} in brain for 7 days, head-only exposure, animals restrained	Significant decrease in CO activity in frontal and posterior cortex, hippocampus and septum at 6 W kg^{-1} only, no effects at lower SAR	Changes in brain metabolism indicative of decreased neural activity
Maskey et al, 2010a	GFAP and calbindin D-28-k (CB) expression using IHC, apoptosis using TUNEL, in ICR mouse hippocampus	835 MHz CDMA, 8 h/day for 3 months at 1.6 W kg^{-1}, animals freely moving, exposed in home cages	Significant increase in GFAP, significant decrease in CB in most areas, with an increase in apoptosis	–
Maskey et al, 2010b	Calbindin D-28-k (CB) and calretinin (CR) expression in ICR mouse hippocampus, using IHC	835 MHz CDMA, 1 h/day for 5 days or 5 h at 1.6 or 4 W kg^{-1} or 1 h/day for 1 month at 1.6 W kg^{-1}, animals freely moving, exposed in home cages	Loss of pyramidal cells in CA1 after 1 month of exposure, significant, but variable, changes seen in CB and CR in all groups, in different cell layers	No obvious trends to responses
Bas et al, 2009a	Pyramidal cell numbers in Wistar rat hippocampus, using optical fractionator technique	900 MHz GSM, 1 h/day for 28 days at 0.016 W kg^{-1}, 2 W kg^{-1} in head, head-mainly exposure, animals restrained	Significant decrease in pyramidal cell numbers, increase in dark neurons	Animals aged 12 weeks at start: considered developmentally equivalent to teenagers
Sonmez et al, 2010	Purkinje cell numbers in Wistar rat cerebellum, using optical fractionator techniques	900 MHz, CW, 1 h/day for 28 days at 0.016 W kg^{-1}, 2 W kg^{-1} in head, head-mainly exposure, animals restrained	Significant decrease in number of Purkinje cells	Also no effect on body or brain weights
Nittby et al, 2008a	Gene expression and gene ontology analysis in Fischer 344 rat cortex (Cx) and hippocampus (CA) using microarrays, 1 h after exposure	1800 MHz GSM, 6 h at 0.03 W kg^{-1}, animals confined in small anechoic chamber	No significant changes in gene expression. 25 (Cx) and 20 (CA) gene categories significantly altered, very small changes considered significant (<0.95- and >1.05-fold)	–

TABLE 4.1 *Continued*

Study	Model used	Exposure conditions	Results of exposure	Comments
Yan et al, 2008, 2009	Expression of Ca-ATPase, neural cell adhesion molecule, neural growth factor (NGF), and vascular endothelial growth factor (in brain) or endothelin (in nerves), reverse transcription PCR, in brain or facial nerves of SD rats	1.9 GHz or 800 MHz CDMA, 6 h/day (2 x 3 h with 30-min interval) for 7 days/week for 18 weeks at 0.9–1.8 W kg^{-1}, from mobile phone, animals restrained	mRNA levels up-regulated (not quantified) in brain and mandibular nerve, Ca-ATPase and NGF unregulated in buccal nerve	Phone held 1 cm from head, SAR measured at 2.2 cm
Sokolovic et al, 2008	Malondialdehyde (MDA) carbonyl group content, catalase (CAT) and xanthine oxidase (XO) activity in Wistar rat brain	900 MHz GSM, 4 h/day for 20, 40 or 60 days at 0.043–0.135 W kg^{-1}, from mobile phone, animals freely moving	MDA significantly increased, carbonyl group increased, CAT decreased at all times, XO increased after 40 and 60 days	Exposures would be highly variable Daily melatonin injection reduced effects
Ilhan et al, 2004	MDA, nitric oxide (NO), superoxide dismutase (SOD), GPx, xanthine oxidase (XO), adenosine deaminase (ADA) activity in Wistar rat brain	900 MHz GSM, 1 h/day for 7 days at 2 W kg^{-1} peak in brain, from mobile phone, animals restrained	MDA, NO, XO and ADA significantly increased, significantly increased numbers of dark neurons	Daily oral gavage of ginkgo biloba mainly reduced effects
Çetin Sorkun et al, 2009	Nucleolar organiser region protein counts by argyrophil (AgNOR) technique, in Wistar rat choroid plexus, ependyma, hippocampus, cortex	900 MHz GSM: (a) 5 x 30 min/day for 3 months from mobile phone in talk mode, (b) 5 x 0.5 min/day for 3 months from phone while ringing, at 1.4 W kg^{-1} in brain, animals restrained	Exposure significantly increased counts in all regions, and significantly more counts in (a) than (b), except in cortex	Sham exposure increased counts in all areas compared with cage controls, difference was significant in ependyma Technique largely superseded by IHC
İmge et al, 2010	MDA, ADA, XO, SOD, GPx, catalase (CAT), 5'-nucleotidase (5'-NT), in Wistar rat brain	900 MHz GSM, at 0.95 W kg^{-1} from mobile phone in standby mode and 4 x 10 min calls/day for 4 weeks, animals freely moving in group	Significant decrease in CAT, 5'-NT	Dosimetric basis of reported SAR value unclear, phones placed 10 cm above the cages Some animals also given vitamin C to measure protective role
Yimaz et al, 2008	Bcl-2 protein in SD rat brain	900 MHz GSM, 20 min/day for 1 month at 0.29-0.87 W kg^{-1}, from mobile phone, animals restrained	No significant effects	Also no effects on testes

Study	Model used	Exposure conditions	Results of exposure	Comments
Arendash et al, 2010	DNA repair enzymes, SOD, glutathione, protein oxidation in transgenic AβPPsw mouse brain, at 9.5 months of age	918 MHz GSM, 2 x 1 h/day from 2 months of age for 7 months at 0.25–1.0 W kg^{-1}, single animals in home cages	No consistent effects in hippocampus of transgenic or normal mice	Dosimetry not well described Also significant improvements in spatial working memory reported
Daşdağ et al, 2008	Phospholipid analysis MDA, p53 activity, histopathology in SD rat brain	900 MHz GSM, 20 min/day for 1 month at 0.29–0.87 W kg^{-1}, from mobile phone, animals restrained	Significant increase in MDA	–
Daşdağ et al, 2009	Caspase-3, p53, CAT, total antioxidant capacity, total oxidant status (TOS) in Wistar rat brain	900 MHz GSM, 2 h/day for 10 months at 0.17–0.58 W kg^{-1}, head-only exposure, animals restrained	Significant decrease in caspase-3, increase in CAT and TOS	Semi-quantitative scoring of caspase-3, suggesting field-induced reduction in apoptosis
Seaman and Phelix, 2005	Ultrastructure of spiny neurons in SD rat caudate-putamen, with injection of 3-nitopropionic acid (3-NP, 10 mg kg^{-1}), 2–3 h after exposure, by light and electron microscopy	1.25 GHz, 5.9 μs pulses, 10 Hz, for 30 min/day for 2 days at 0.6 or 6 W kg^{-1}, animals minimally confined	Effects seen with 6 W kg^{-1} alone Effects of 3-NP significantly increased with 6 W kg^{-1}, significantly reduced with 0.6 W kg^{-1}	Higher SAR hyperthermic No effects on motor activity or inhibition of acoustic startle
Tarantino et al, 2005	Body weight, morphology and apoptosis in New Zealand and California rabbit brain, 12 or 18 months after exposure, by light and electron microscopy	650 MHz, 24 h/day for 2 years, at 3.8 W kg^{-1}, animals freely moving in home cages	No effect on weight or pathological changes, progressive change in brain morphology, and increase in apoptosis	Also highly significant changes in liver and spleen, mainly after 18 months Basis of dosimetry not presented
Ozgur et al, 2010	MDA, total nitric oxide (NO_X), SOD, GPx, myeloperoxidise (MPO), in liver of guinea pigs, by spectrophotometry	1800 MHz GSM, at 0.38 W kg^{-1} for 10 or 20 min/day for 7 days, animals freely moving	Significant increase in MDA and NO_X, significant decrease in SOD, GPx and MPO Increase in MDA and NO_X after 20 min significantly larger than after 10 min	Animals injected with 1 ml saline intraperitoneal 30 min before exposure Some animals also injected with antioxidants to measure protective role

TABLE 4.2 Animal studies investigating effects on neurotransmitters in the brain and nervous tissue

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Mausset-Bonnefont et al, 2004	Binding properties of NMDA and $GABA_A$ receptors and dopamine transporters, expression of NMDA subunits, in Wistar rat brain, 3 days after exposure, by autoradiography and Western blot	900 MHz GSM, 15 min at 6 W kg^{-1}, head-only exposure, animals restrained	Significant changes in specific binding and binding parameters, significant decrease in post-synaptic NMDA receptor subunits	No significant effects on locomotory behaviour in open field Temperature rise in the head <0.5°C
Crouzier et al, 2007	Acetylcholine (ACh) in SD rat hippocampus during exposure, by microdialysis using implanted cannula	1800 MHz GSM, 24 h at 0.07 or 0.53 W kg^{-1} in head, animals freely moving in anechoic chamber	No significant effects on ACh release	Animals in chamber for 3 days, exposed on middle day, animals implanted with electrodes and thermistor

TABLE 4.3 Animal studies investigating effects on electrical (and seizure) activity in the brain and nervous tissue

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Vorobyov et al, 2004, 2010	EEG in cortex, hypothalamus of Wistar rats, in 20 narrow frequency bands	915 MHz pulsed, 20 ms pulse, 4 Hz, intermittent (1 min on/ 1 min off) for 3 x 10 min/day, for 3 days, at 0.7 W kg^{-1}, animals freely moving in anechoic chamber, rotated into preferred orientation when asleep	Significant increase in $beta_2$ activity (17.8–3.5 Hz) in hypothalamus, increased with exposure, less consistent increase in cortex, mediated by increases in ACh activity	Carbon electrodes implanted in hypothalamus or cortex Peak SAR 'much higher'
Crouzier et al, 2007	EEG (delta and theta bands), electromyogram (EMG), sleep stage, skin temperature in SD rats during exposure, and lipids in brain by MRI	1800 MHz GSM, 24 h at 0.07 or 0.53 W kg^{-1} in head, animals freely moving in anechoic chamber	No significant effects	Animals in chamber for 3 days, exposed on middle day, animals implanted with silver electrodes, thermistor and cannula
Lipping et al, 2009	EEG in deeply anaesthetised pigs, during exposure	890 MHz GSM, 1–10 s bursts for 10–20 min at 7.3 or 31 W kg^{-1} in head or 10 mins at 31 W kg^{-1} in head, using dipole antenna	No significant effects on provoking burst activity in EEG No effects of continuous exposure on power of frequency bands	Skin temperature increased by 1–2°C and heart rate increased by about 14 bpm
López-Martin et al, 2006, 2009	EEG in SD rat brain made seizure-prone with picrotoxin (2 mg kg^{-1})	900 MHz GSM or CW, 2 h at 0.03–0.05 or 0.27–0.42 W kg^{-1} in brain (GSM) or 0.26 W kg^{-1} in brain (CW), animals restrained	GSM induced seizure activity, no changes without picrotoxin or with CW	5 steel screws inserted into skull as electrodes
Erdinc et al, 2003	Pentylenetetrazole (PTZ)-induced seizure activity in 3 and 6 week old albino mice after exposure	900 MHz, 2 or 20 h at 0.25 mW (SAR not given) using dipole antenna in basket-box	Significantly reduced onset of facial twitching and mild myoclonic movements in younger mice after 20 h, no effect on more severe signs or on mortality	Seizure activity scored by observation, not by EEG

TABLE 4.4 Animal studies investigating effects on the blood-brain barrier and changes in microcirculation in the brain

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Kuribayashi et al, 2005	Permeability to albumin using FITC-dextran, in 4 or 10 week old Fisher 344 rat, expression of claudin-5, auaporine-4, p-glycoprotein, by immunohistochemistry (IHC), q RT-PCR, pathological changes	1.439 GHz PDC, 6.7 ms pulses at 50 pps, 90 min/day, 6 days/week for 1 or 2 weeks at 2 or 6 W kg^{-1} in brain	No significant effects on permeability or gene expression	1,3-dinitrobenzene (10 mg kg^{-1}) increased leakage and decreased gene expression
Cosquer et al, 2005a	Performance in radial arm maze by SD rat, injection of scopolamine methylbromide before or after exposure (0.5 mg kg^{-1}), permeability to Evans blue	2.45 GHz pulsed, 2 μs pulses, 500 pps, 45 min/day for 10 days at 2 W kg^{-1}, animals confined in circular waveguide	No significant effects on maze performance No increased leakage	Cold injury positive control yielded effects
Finnie et al, 2006b,c	Permeability to Evans blue in near-term, neonatal BALB/c mouse brain, using IHC	900 MHz GSM, 60 min/day on gestational days 1–19 or on postnatal days 1–7 at 4 W kg^{-1}	No significant effects on albumin leakage	Chemical control gave positive results
Kumlin et al, 2007	Permeability to Evans blue in immature Wistar rat brain	900 MHz GSM, 2 h/day, 5 days/week for 5 weeks at 0.3 or 3 W kg^{-1}, animals freely moving	No significant effects on leakage	Examined in 35 μm sections
Sirav and Seyhan, 2009	Permeability to Evans blue in Wistar rat brain, anaesthetised with ketamine (45 mg kg^{-1}) and xylazine (5 mg kg^{-1})	900 or 1800 MHz, CW, 20 min at 12–13 V m^{-1}, animals 10 cm from horn antenna	Significant increase in leakage in males, not in females	No SAR given Results in males attributable to depressed sham values (compared with females)
Grafström et al, 2008	Permeability to albumin, in Fischer 344 rat brain, 5–7 weeks after exposure, by IHC	900 MHz GSM, 2 h/week for 55 weeks at 0.0006 or 0.06 W kg^{-1}, animals confined in TEM cell	No significant effects on albumin leakage	SAR reduced over time due to animal growth, by x0.3 at end Animals used in behavioural studies by Nittby et al, 2008b

Study	Model used	Exposure conditions	Results of exposure	Comments
Eberhardt et al, 2008	Permeability to albumin in Fischer 344 rat brain, 14 or 28 days after exposure, by IHC, cresyl violet stain	900 MHz GSM, 2 h at 0.00012, 0.0012, 0.012 or 0.12 W kg^{-1}, animals confined in TEM cell	Significant increase in leakage and neuronal uptake of albumin on day 14, not on day 28; significant increase in dark neurons on day 28	No voice modulation Inverse dose-response
Nittby et al, 2009	Permeability to albumin in Fischer 344 rat brain, 7 days after exposure, by IHC	900 MHz GSM, 2 h at 0.00012, 0.0012, 0.012 or 0.12 W kg^{-1}, animals confined in TEM cell	Significant increase in leakage at 0.012 W kg^{-1}	No voice modulation
McQuade et al, 2009	Permeability to albumin in Fischer 344 rat brain, by IHC, 10–15 min after exposure	915 MHz, CW, or 915 MHz pulsed at 16 or 217 Hz, 30 min at 0.0018– 20 W kg^{-1}, animals confined in top compartment of TEM cell	Little or no extravasations in all groups	Urea infusion and hyperthermia yielded large effects
Masuda et al, 2009	Permeability to albumin in Fischer 344 rat brain, by IHC, cresyl violet, H&E, 14 or 50 days after exposure	915 MHz pulsed at 16 or 217 Hz, 2 h at 0.02, 0.2, or 2 W kg^{-1}, animals confined in top compartment of TEM cell	No extravasations, no significant increase in dark neurons, no morphological changes in cells	Cold injury and kainic acid used as positive controls: both yielded large effects Does not confirm results of Salford et al, 2003
Poulletier de Gannes et al, 2009a	Permeability to albumin in Fischer 344 rat brain, by IHC, FluroJade B, TUNEL, 14 or 50 days after exposure	915 MHz GSM, 2 h at 0.14 or 2 W kg^{-1} in brain, head-only exposure, animals restrained	No significant increase in leakage and dark neurons in 12 different regions of the brain No apoptosis detected after 14 days	Cold injury used as positive control produced significant changes Does not confirm results of Salford et al, 2003
Masuda et al, 2007a,b; Hirota et al, 2009	Venule diameter, plasma velocity, leukocyte behaviour, permeability to fluorescein, dextran, in SD rat brain using fluorescence microscopy via closed cranial window, 20 min or 24 h after exposure	1.439 GHz PDC, 6.7 ms pulses at 50 pps, 10 min at 0.6, 2.4 or 4.8 W kg^{-1} in brain or 60 min/day, 5 days/week for 4 weeks at 2.4 W kg^{-1} in brain, head-mainly exposure	No significant effects of acute or repeated exposure	Animals were anaesthetised during exposure and observation

TABLE 4.5 Animal studies investigating effects on autonomic function

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Millenbaugh et al, 2006	Blood pressure, heart rate, skin and core temperatures (T_c) in SD rats, anaesthetised with ketamine/xylazine or isoflurane during exposure	35 or 94 GHz, CW, 75 or 90 mW cm^{-1} in anechoic chamber, 42 or 43°C in environmental heating chamber	No effects on heart rate 94 GHz at 90 mW cm^{-1} significantly reduced time to collapse and reduced T_c All RF increased size and rate of temperature rise in skin	Exposures matched to produce same core heating rates Circulatory collapse indicated by mean arterial pressure < 20 mm Hg
Li et al, 2007	Heart rate and blood pressure in SD rats, measured after exposure to EMP and for up to 4 weeks, using tail-cuff sphygmomanometer	0.5 pps, total 200 pulses, 0.5 W kg^{-1} at 200 kV m^{-1}, or 0.75 W kg^{-1} at 400 kV m^{-1}, in GTEM cell, animals restrained	No effects on heart rate, blood pressure significantly increased immediately, decreased after 6 h for 4 weeks No evidence of dose-response	Animals habituated to holders

4.1.6 Summary

Research has continued to investigate the possible effects of RF fields on the brain and nervous system in animals, and a substantial number of studies have been published since 2003 using a variety of models.

Studies investigating effects on cellular physiology have produced some evidence to suggest that low level exposures are capable of causing measurable biological changes, although the possibility remains that these effects represent responses to subtle heating. In particular, the reported changes in GFAP which suggest that exposure may engender inflammatory or other protective measures above a given threshold (between 1.5 and 6 W kg^{-1}) clearly raise the possibility of a mild heating phenomenon. One recent study suggests that three major neurotransmitter systems can be affected by acute exposure of the head of rats to GSM signals. The exposures were above guideline values, although heating was considered to be minimal. In addition, most recent studies provide no clear evidence of field-dependent effects on the electrical activity of the brain. However, one study suggests that animals made prone to epilepsy may show increased sensitivity to exposure.

The majority of recent studies investigating effects on the blood-brain barrier have reported robustly negative results. Importantly, the observations of Salford and colleagues could not be confirmed by three independent research groups, and the positive results have been largely attributed to technical shortcomings and the presence of artefacts. Overall, the evidence for low level effects on the blood-brain barrier has grown substantially weaker since 2003, and it now seems far less likely that low level fields are capable of causing detrimental changes.

Finally, very few recent studies have investigated effects on autonomic functions. One study showed that although very high frequency fields cause greater heating in the skin, these fields induce the same thermoregulatory responses as caused by warm environments.

4.2 Behaviour

It has long been recognised that exposure of animals to RF fields at thermal levels may affect their behaviour and disrupt performance of learned tasks, but this does not exclude the possibility that low level exposures may engender subtle behavioural or cognitive changes under certain circumstances. AGNIR (2003) concluded that while no field-dependent effects have been firmly established in the absence of heating, the available evidence was limited, and the long-term consequences of exposure on immature animals had not been sufficiently researched. Recent behavioural work has tended to concentrate on the spatial learning abilities of adult rodents, although a few studies with immature animals have been undertaken.

4.2.1 Spatial memory tasks

A number of studies have investigated the effects of RF fields on spatial memory and place learning tasks in rodents (Table 4.6) mainly using radial arm mazes (Figure 4.2) or water mazes (Figure 4.3). These follow earlier reports from one laboratory suggesting that large field-dependent deficits in behaviour may occur (Lai et al, 1994; Wang and Lai, 2000), although independent studies were not able to support these findings in either rats or mice (AGNIR, 2003).

Text continues on page 140

TABLE 4.6 Animal studies investigating effects on place learning and spatial memory tasks

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Cobb et al, 2004	Performance of SD rats in 12-arm radial maze, limited access to distal spatial cues	2.45 GHz, pulsed 2 μs, 500 pps, 45 min/day for 10 days at 0.6 W kg^{-1}, animals confined within circular waveguide, exposed just before trial	No significant differences in errors or time Pre-injection with naltrexone or physostigmine (1 mg kg^{-1}) significantly increased time	Physostigmine close to lethal dose Did not confirm results of Lai et al, 1994
Cassel et al, 2004 ; Cosquer et al, 2005a,b	Performance of SD rats in 12-arm radial maze, with access or limited access to distal spatial cues, precision pellets or small lumps of cheese used as reinforcement	2.45 GHz, pulsed 2 μs, 500 pps, 45 min/day for 10 days at 0.6 or 2 W kg^{-1} , animals confined within circular waveguide, exposed just before trial	No significant differences in errors made, errors in first 12 choices or in number of arms visited before first error Pre-injection with scopolamine hydrobromide (10 or 50 min, 0.5 mg kg^{-1}) significantly increased errors, no effect with scopolamine methylbromide before or after exposure	Did not confirm results of Lai et al, 1994
Ammari et al, 2008c	Performance of SD rats in 8-arm radial maze over 10 days and then 8 days with 45 min inter-trial delay (ITD) after 4 correct responses, access to distal spatial cues	900 MHz GSM, 45 min/day at 1.5 W kg^{-1} or 15 min/day at 6 W kg^{-1}, both in brain, 5 days/week for 8 or 24 weeks, head-only exposure, animals restrained, testing towards end of exposure periods	Isolated significant differences, but no consistent effects on number of correct responses, errors made, number of arms visited before first error, time to complete task	Scopolamine (1 mg kg^{-1}) significantly increased numbers of errors and time with ITD Evidence of poorer performance in cage controls due to lack of daily handling
Nittby et al, 2008b	3 trial object/place recognition memory test in Fisher 344 rats 5–6 weeks after exposure	900 MHz GSM, 2 h each week for 55 weeks at 0.0006 or 0.06 W kg^{-1}, animals confined in TEM cell	Small, but significant change in exploratory behaviour, but effect far greater in cage controls No effect on exploring objects in novel locations	No voice modulation SAR at start of experiment reduced by 30% due to animal growth Effects on blood-brain barrier reported by Grafström et al, 2008

TABLE 4.6 *Continued*

Study	Model used	Exposure conditions	Results of exposure	Comments
Narayanan et al, 2009	Performance of Wistar rats in Morris water maze, 7 sessions over 4 days, probe trial 24 h later	900/1800 MHz GSM, 50 missed calls/day for 4 weeks from mobile phone (silent mode but with vibration), each call lasted 1 min, interval of 15 s, animals freely moving	Escape latency significantly increased throughout acquisition trials, during probe trail, time in target quadrant significantly decreased	SAR not given Rat released into maze facing wall, except in quadrant with hidden platform
Fragopoulou et al, 2010a	Performance of BALB/c mice in Morris water maze, 4 trials/day for 4 days, probe trial 2 h later	900 MHz GSM, 1 h 55 min for 3 days, then 3 h 45 min for last day, estimated at 0.41–0.98 W kg^{-1} in brain, from mobile phone under home cage, animals freely moving	No overall changes, but latency and distance significantly increased on trial 1 on days 2, 3 and 4 No preference for target quadrant during probe trial in either time spent or distance swam	Animals exposed before each block of trials, as well as in between and after each trial, and before probe trial Start position in maze not randomised
Lai, 2004	Performance of SD rats in Morris water maze, 2 x 4 trials/day for 3 days, probe trial 1 h later	2.45 GHz, CW, 1 h at 1.2 W kg^{-1} and/or 30–100 Hz magnetic field at 6 μT (noise)	CW significantly increased escape times, CW plus noise significantly reduced effect, CW significantly decreased time in platform quadrant during probe trial	Copper waveguide used, noise not attenuated
Kumlin et al, 2007	Performance of Wistar rats in Morris water maze, 4 trials/day for 4 days, probe trial 24 h later	900 MHz GSM, 2 h/day from postnatal day 24 for 5 days/week for 5 weeks at 0.3 or 3 W kg^{-1}, animals freely moving	Improved performance: significantly decreased escape times, significantly increased time in platform quadrant during probe trial at 3 W kg^{-1}	Also no effects on brain morphology, numbers of dark neurons or on blood-brain barrier permeability
Daniels et al, 2009	Performance of SD rats in Morris water maze, 4 trials followed by 2 test trials and probe trial, open field test, on postnatal day 58–62	840 MHz, 3 h/day from postnatal day 2–14 at power density of 60 μW m^{-2}, animals freely moving with mothers, arranged to face antenna	No effects on performance, but significantly increased freezing behaviour by males only, males displayed significantly increased grooming and significantly less locomotion in open field	No estimate of SAR No morphological effects on hippocampal cells, or on corticosterone levels

Study	Model used	Exposure conditions	Results of exposure	Comments
Arendash et al, 2010	Repeat performance of transgenic AβPPsw (Tg) and non-transgenic (NT) mice during exposure, on radial arm water maze (RAWM) for 5 trials/day for 6, 10 or 14 days, and on cognitive interference task (CIT) version of RAWM for 5 trials/day for 4 days Spontaneous alternation in Y-maze for 5 min, or stress-anxiety test battery and amyloid β (Aβ) by IHC or Enzyme Linked ImmunoSorbent Assay (ELISA) in hippocampus and cortex after exposure	918 MHz GSM, 2 x 1 h/day at 0.25–1.0 W kg^{-1} in brain: (a) from 2 months old for 7 months, (b) from 5 months old for 8 months, animals unrestrained in home cages with food and water, singly housed	(a) RAWM over 10 days: no differences after 2.5 months, CIT: no differences after 4–5 months, fewer errors in Tg exposed after 6–7 months compared with Tg sham, Y-maze: more alternations by NT exposed compared with other groups (b) RAWM over 6 days: more errors by Tg pre-exposure, RAWM over 14 days: more errors in Tg sham and exposed after 2 months compared with NT sham and exposed, CIT: fewer errors in NT exposed after 5 and 8 months compared with NT shams, fewer errors in Tg exposed compared with Tg sham after 8 months, Aβ burden less in Tg exposed compared with Tg sham Rectal temperature increased by >1 °C in Tg exposed	All differences here are statistically significant Elevated brain temperature could be key, but exposure system and dosimetry not fully described Also no consistent effects on DNA repair enzymes, and markers of oxidative stress largely unaffected after 7 months of exposure (a)
Dragicevic et al, 2011	Respiratory function of total mitochondria, cytochrome c oxidase using oxygen electrode, ROS, mitochondrial membrane potential by fluorescence, soluble Aβ1-40 by ELISA, ATP levels, in cerebral cortex, hippocampus, striatum, amygdala of transgenic AβPPsw (Tg) and non-transgenic (NT) mice, after exposure	918 MHz GSM, 2 x 1 h/day at 0.25–1.05 W kg^{-1} for 1 month at 15–17 months old, animals unrestrained in home cages with food and water, singly housed	Significant differences between Tg and NT in all measures Compared with unexposed, Tg mice had significantly increased respiratory rates, membrane potentials, cytochrome c oxidase, Aβ1-40, ATP, significantly reduced ROS, mainly in cortex and hippocampus Lesser effects seen in NT	Exposure system and dosimetry not fully described Body temperature significantly increased, but not brain temperature

TABLE 4.7 Animal studies investigating effects on innate and learned behaviours (excluding spatial memory)

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Mausset-Bonnefont et al, 2004	Open field behaviour of Wistar rats immediately or 24 h after exposure	900 MHz GSM, 15 min at 6 W kg^{-1}, head-only exposure, animals restrained	No significant effects on locomotion or grooming	Significant increase in expression of GFAP and neurotransmitters
Nittby et al, 2008b	Open field behaviour of Fischer 344 rats 3–4 weeks after exposure	900 MHz GSM, 2 h each week for 55 weeks at 0.0006 or 0.06 W kg^{-1}, animals confined in TEM cell	No significant effects, sex-related differences and cage controls showed less habituation	No voice modulation Effects on blood-brain barrier reported by Grafström et al, 2008
Daniels et al 2009	Open field behaviour of SD rats on postnatal day 58–62	840 MHz, 3 h/day from postnatal day 2–14 at power density of 60 μW m^{-2}, animals freely moving with mothers, arranged to face antenna	Significantly increased grooming and significantly less locomotion in males	No estimate of SAR No effects on spatial memory
Cosquer et al, 2005c	Behaviour of SD rats in an elevated-plus maze, under 2.5 or 30 lux ambient light	2.45 GHz, pulsed 2 μs, 500 pps, 45 min at 0.6 W kg^{-1}, animals confined within circular waveguide	No significant change in percentage of open arm entries or percentage time in open arms Significantly higher anxiety in naïve rats under 2.5 lux	Reduced anxiety with low ambient light (<10 lux) or diazepam (0.5 or 1 mg kg^{-1})
Kumlin et al, 2007	Open field behaviour, elevated-plus maze, acoustic startle of Wistar rats	900 MHz GSM, 2 h/day from postnatal day 24 for 5 days/week for 5 weeks at 0.3 or 3 W kg^{-1}, animals freely moving	No significant effects	–
Kumar et al, 2009	Elevated-plus maze behaviour of Wistar rats, 1 and 24 h after last exposure	900/1800 MHz GSM, 50 missed calls/day for 4 weeks (1 min duration, 15 s interval), animals freely moving in home cage, phone placed in box in cage	Significantly decreased exploration of open arms, significantly increased defecation	Preliminary study only No dosimetry, phone in vibratory mode, but no ring tone Numbers in exposed groups ($n = 3$) too small

Study	Model used	Exposure conditions	Results of exposure	Comments
Rocha et al, 2009	Weight of Norway rats at 10, 70 and 100 days of age, behaviour in elevated-plus maze, water maze at 30, 60 and 90 days of age, daily food, water consumption (age not specified)	850 MHz, CW, 60 min/day 'since gestation' until 100 days old, at 6 W m^{-2}, animals freely moving in home cage; not clear if prenatal exposures occurred	Small increase in water intake, reduced level of anxiety (except in 60 day old females)	Dosimetry very poor, statistical analysis weak, non-standard water maze protocol, plus maze very small (70 cm diameter)
Narayanan et al, 2010	Passive avoidance of Wistar rats, consisting of 3 habituation trials, foot shock association trial, and retention trials at 24 and 48 h	900/1800 MHz GSM, 50 missed calls/day for 4 weeks from mobile phone (silent mode but with vibration), each call lasted 45 s, interval of 15 s, animals freely moving	Significantly increased latency to enter dark compartment during habituation trials 2 and 3 and during both retention trials	Changes in hippocampal morphology Phone in cage, but beneath 'bamboo wire mesh'
Ntzouni et al, 2011	Recognition memory task of C57BL/6 mice, measured using a discrimination index (DI)	1800 MHz GSM, 5 or 10 min/day for 3 days during trials in arena, 90 min/day for 32 days in home cage (task begun on day 17 of exposure) at 0.22 W kg^{-1} in brain, mobile phone under arena/cage, animals freely moving	No significant effects with acute exposure in arena, DI significantly reduced following repeated exposures and during inter-trial interval, no significant effect 24 h after repeated exposure	Radio station playing in background to simulate human voice during exposures

4.2.3 Summary

Studies have continued to investigate the effects of low level RF fields on cognitive function and behaviour in animals, with particular emphasis on spatial memory functions. Taken together, the evidence for any field-dependent effects is not strong, but relatively few models and signals have been investigated. Very few studies have yet been performed with immature or juvenile animals.

Two laboratories tried unsuccessfully to replicate earlier reports of field-dependent changes in spatial memory in adult rats exposed to pulsed 2.45 GHz fields, and another study reported no changes in behaviour using mobile phone signals. Some studies have reported field-dependent behavioural changes, although the evidence from these studies is considered weak, primarily because they used a mobile phone as an exposure system. This would have resulted in uncontrolled and highly variable amounts of energy being absorbed by the animals, and an overall lack of knowledge about the exposure. A keystone of all scientific laboratory work is in the control of experimental factors, allowing the possibility of replication and repeatability of the observed result.

Three studies present particularly intriguing results: one reported that performance in a water maze could be improved following medium-term exposure of juvenile animals; another suggested that long-term exposure may protect against age-related behavioural deficits in a transgenic mouse model of Alzheimer's disease, and provide cognitive enhancing effects in normal mice; and the third reported that behavioural impairments associated with short-term exposure could be inhibited by exposure to incoherent magnetic field noise. However, further studies are needed for all of these results before any firm conclusions can be drawn. Studies with the transgenic mouse model and using juvenile animals would be of particular interest and importance.

It has been suggested that low level RF fields could increase levels of anxiety, and so lead to behavioural or other changes. However, a well-performed study found no evidence that pulsed 2.45 GHz fields had any effect on anxiety as measured using an elevated-plus maze.

4.3 Endocrine System

Previous animal studies have indicated that the most consistent changes in endocrine function occur with acute exposures to RF fields that increase core body temperature by about 1 °C or more; changes in the absence of such temperature rises have not been reliably demonstrated. Historically, most work seems to have been performed on the hormones associated with the hypothalamic-pituitary-adrenal axis, possibly due to their roles in stress and metabolism. Recent research has centred on the effects of mobile phone signals on melatonin, a hormone secreted largely by the pineal gland at night (Table 4.8).

4.3.1 Melatonin

Bakos et al (2003) found that repeated, acute exposure of male rats to GSM signals in the early light phase had no significant effect on the daily urinary excretion levels of the major metabolite of melatonin. Hata et al (2005) reported that short-term exposure to TDMA signals during the dark phase had no effect on serum or pineal melatonin levels in male rats. Koyu et al (2005a) reported that daily, acute exposure to

TABLE 4.8 Animal studies investigating effects on endocrine function

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Bakos et al, 2003	Excretion of 6-sulfatoxymelatonin in Wistar rats by radioimmunoassay (RIA), referred to creatinine, urine collected 12:00 to 08:00 h on alternate days	900 or 1800 MHz GSM, 2 h/day (from 08:00 or 10:00 h) for 14 days at 0.009–0.012 W kg^{-1} (900 MHz) or 0.022–0.045 W kg^{-1} (1800 MHz), animals freely moving in groups of 6	No significant effects (although initial values for exposed and sham groups significantly less with 900 MHz)	Lights on from 06:00–18:00 h Signal without voice modulation
Hata et al, 2005	Nocturnal pineal melatonin and serotonin levels, serum melatonin levels in SD rats, by RIA, 30 min or 6 h after exposure	1439 MHz TDMA, 4 h (from onset of dark) at 2 W kg^{-1}, 7.5 W kg^{-1} in head, animals restrained	No significant effects	Lights on from 20:00–08:00 h (reversed day-night) Significant suppression of melatonin and increase in serotonin shown using light control (400 lux)
Koyu et al, 2005a	Nocturnal serum melatonin levels in SD rats, by RIA, at end of exposure	900 or 1800 MHz, CW, 30 min/day, 5 days/week for 4 weeks at 2 W kg^{-1} (peak), animals restrained	No significant effects	Time of exposure each day not given Melatonin assayed at 24:00 h
Lerchl et al, 2008	Nocturnal serum and pineal melatonin levels in Djungarian hamsters, by RIA, at end of exposure	900 or 1800 MHz GSM or 383 MHz (TETRA), 24 h/day for 60 days at 0.08 W kg^{-1}, animals freely moving	No significant effects	Photoperiod of 16 h light and 8 h dark Significant increase in body weight with 383 and 900 MHz
Koyu et al, 2005b	Serum thyroid stimulating hormone (TSH), triiodothyronine (T_3) and thyroxin (T_4) levels in SD rats, by RIA, at end of exposure	900 MHz, CW, 30 min/day, 5 days/week for 4 weeks at 2 W kg^{-1} (peak), animals restrained	Significant decrease in TSH, T_3 and T_4	Animals exposed at 10:00–11:00 h

Study	Model used	Exposure conditions	Results of exposure	Comments
Eşmekaya et al, 2010	Thyroid morphology, apoptosis in Wistar rats, by light and electron microscopy, immunohistochemistry (IHC), after exposure	900 MHz, rectangular pulses 217 Hz, 0.573 ms, 20 min/day for 3 weeks at 1.35 W kg^{-1}, animals freely moving, possibly as a group	Morphological changes seen, with significant increase in follicle and colloid diameters and areas Significantly increased activity of caspase-3 and caspase-9	Rectal temperature increased by 0.2°C IHC staining scored subjectively
Yamashita et al, 2010	Serum oestradiol levels, in ovariectomised SD rats, by RIA, 1 day after exposure	1439 MHz PDC, 4 h/day for 3 days at 0.88–0.99 W kg^{-1}, 5.5–6.1 W kg^{-1} in brain, animals restrained	No significant effects	Significant effect with injected 17β-oestradiol (100 μg kg^{-1} per day)
Meo et al, 2010	Serum testosterone levels in Wistar rats, by RIA, after exposure	Unspecified signal from a mobile phone, 30 or 60 min/day for 3 months, animals freely moving in groups of 3	Significant decrease after 60-min exposure	SAR would be highly variable, dosimetry lacking

GSM signals for 4 weeks had no effect on serum melatonin levels. Lerchl et al (2008) found that long-term, continuous exposure of Djungarian hamsters to TETRA or GSM signals did not result in significant changes in circulating or pineal melatonin levels.

4.3.2 Other hormones

Koyu et al (2005b) examined the effects of GSM signals on thyroid hormone function in rats. Significantly reduced hormone levels were reported after acute, daily exposures for 1 month, but the authors noted the possibility that increased tissue temperatures may have contributed to this result. Eşmekaya et al (2010) reported that daily, acute exposure to pulsed 900 MHz signals for 3 weeks induced pathological changes in the thyroid gland of rats, possibly indicative of decreased thyroid hormone secretion, and a significant increase in apoptosis in thyroid cells. Two studies have investigated effects on reproductive hormones. Yamashita et al (2010) found that short-term exposure to PDC signals had no effect on circulating oestradiol levels in ovariectomised rats. Significant decreases in circulating testosterone levels in rats were reported by Meo et al (2010) following daily, 60-minute exposures to signals from a mobile phone for 3 months, but not following 30-minute exposures. However, the absence of any exposure-related information or dosimetry renders this study uninterpretable.

4.3.3 Summary

Several studies have investigated the effects of mobile phone signals on melatonin, but no field-dependent effects have been seen. There is a paucity of information on other hormones.

4.4 Auditory System

Because mobile phones are usually held in close proximity to the ear, concerns have been raised as to whether these exposures could have an adverse effect on hearing and auditory function, either at the level of the inner ear or on the central auditory pathways. Since 2003, a number of animal studies have addressed these issues (Table 4.9).

4.4.1 Experimental studies

Distortion-product otoacoustic emissions (DPOAE) provide a very sensitive, fast and reliable method to determine cochlear (and, specifically, outer hair cell) functionality. In this test, acoustic signals (distortion products) are generated by the cochlear in response to two simultaneous pure tones of different frequencies, and these can be recorded using a sensitive microphone placed in the external auditory meatus. Changes in the characteristics of the DPOAE indicate functional or structural damage to the cochlear.

Kizilay et al (2003) found that DPOAE amplitudes in newborn and adult rats were unchanged following repeated, acute exposure to 900 MHz GSM signals. Aran et al (2004) found the same result in guinea pigs; auditory evoked potential thresholds were also unchanged in this study.

Text continues on page 156

TABLE 4.9 Animal studies investigating effects on auditory function

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Kizilay et al, 2003	DPOAE (1–6.3 kHz) in newborn and adult SD rats anaesthetised by injection, measured before and after exposure	900 MHz GSM, 1 h/day for 30 days at 0.95 W kg^{-1}, animals restrained	No significant differences between treatment groups or following exposure	Newborns exposed from postnatal day 2 Otomicroscopy revealed no pathologies
Aran et al, 2004	DPOAE (0.5–8 kHz) auditory brainstem responses (ABR), cochlear histology, in guinea pigs anaesthetised by injection, before and after exposure, and 2 months later	900 MHz GSM, 1 h/day, 5 days/week for 2 months at 1, 2 or 4 W kg^{-1}, left ear only, animals restrained	No consistent differences between left and right ears, or between treatment groups Also no effects on ABR following acute exposure (2 h at 4 W kg^{-1})	Time of daily exposure systematically rotated ABR thresholds significantly increased with time
Galloni et al, 2005a	DPOAE (3–7 kHz) in SD rats anaesthetised by inhalation, measured before, after each week of exposure, and up to 1 week after exposure	960 MHz GSM, or 936 or 923 MHz, CW, 3 h/day for 5 days at 1 W kg^{-1} in ear, or 900 MHz GSM, 2 h/day, 5 days/week for 4 weeks at 2 W kg^{-1} in ear, animals restrained	No significant differences for any treatment group compared with pre-exposure values	–
Galloni et al, 2005b	DPOAE (4–13 kHz) in SD rats anaesthetised by inhalation, before, after each week of exposure, and 1 day and 1 week after exposure	900 or 1800 MHz GSM, 2 h/day, 5 days/week for 4 weeks at 2 W kg^{-1} in ear, only right ear exposed/tested, animals restrained	No significant differences between treatment group	Slight variability in results attributed to changes in recording conditions caused by stress in animals

TABLE 4.9 *Continued*

Study	Model used	Exposure conditions	Results of exposure	Comments
Galloni et al, 2009	DPOAE (3–11 kHz) in SD rats anaesthetised by inhalation, before, after each week of exposure, and 1 week after exposure ceased	1946 MHz UMTS, 2 h/day, 5 days/week for 4 weeks at 10 W kg^{-1} in ear, only right ear exposed/tested, animals restrained	No significant differences between treatment groups at any time point	Significant changes induced by repeated, daily injection with antibiotic, kanamycin (250 mg kg^{-1}), after 4 weeks
Parazzini et al, 2007	DPOAE (3–13 kHz) in SD rats anaesthetised by inhalation, before, after each week of exposure, and 1 week after exposure	900 MHz, CW, 2 h/day, 5 days/week for 4 weeks at 4 W kg^{-1} in ear, daily injections of gentamicin (150 mg kg^{-1}) 1 h before first exposure, for 2 weeks, only right ear exposed/tested, animals restrained	No significant differences at low frequencies tested (<6 kHz) At higher frequencies (7–13 kHz) gentamicin induced significant decreases in DPOAE amplitude, but no additional effect with 900 MHz	Gentamicin is known to affect only higher frequency emissions
Budak et al, 2009a	DPOAE (1–8 kHz) in 1 month old and adult female New Zealand white rabbits anaesthetised by injection, measured in both ears after exposure	1800 MHz GSM, 15 min/day for 7 days at 0.1 W, animals anaesthetised	DPOAE amplitudes significantly increased in young (at 1, 1.5, 2 and 6 kHz) and significantly decreased in adults (at all frequencies)	SAR not given, dosimetry lacking
Budak et al, 2009b	DPOAE (1–8 kHz) in anaesthetised male New Zealand white rabbits, measured in both ears after exposure (age not specified – 6 weeks old?)	1800 MHz GSM, 15 min/day for 7 days on gestation day 15–22 at 0.1 W (pre), 15 min/day for 14 days from 1 month of age at 0.1 W (post) or both exposures (pre+post)	DPOAE significantly increased in pre (at 1.5 kHz), and in pre+post (at 1.5, 3 and 6 kHz), and significantly decreased in post (at 4 and 6 kHz) Compared with post, DPOAE significantly increased in pre+post (at 1.5–6 kHz)	SAR not given, dosimetry lacking on pregnant or young animals

Study	Model used	Exposure conditions	Results of exposure	Comments
Budak et al, 2009c	DPOAE (1–8 kHz) in pregnant and non-pregnant New Zealand white rabbits anaesthetised by injection, measured in both ears after exposure	1800 MHz GSM, 15 min/day for 7 days (gestational days 15–22) at 0.1 W, animals anaesthetised	DPOAE significantly decreased in non-pregnant (at 1–4 kHz) No significant decrease in pregnant (except at 2 kHz)	SAR not given, dosimetry lacking Large variability in results
Kayabasoglu et al, 2011	DPOAE (1–8 kHz) in newborn and adult Wistar rats anaesthetised by injection, before and after exposure	900 or 1800 MHz GSM signal from mobile phones, 6 h/day for 30 days, using carousel system	No significant effects compared with unexposed control animals	SAR not given, dosimetry lacking Outputs of phones rated at 0.85–0.93 W kg^{-1}
Kaprana et al, 2011	Auditory brainstem response to 0.1 ms pulse stimuli, in anaesthetised adult New Zealand rabbits, measured from both ears, during and 24 h after exposure	903 MHz, CW, 60 min to one ear at 0.22 W, animals anaesthetised	Significant delays in latencies of waves III, IV, V after 15, 45 and 60 min, interwave latencies I–V, III–V significantly prolonged after 30 min, ipsilateral side only No effect after 24 h	SAR not given, dosimetry lacking

The effects of mobile phone signals on cochlear function in rats have also been investigated in an extensive series of studies by Marino and colleagues. No significant effects on DPOAE measurements were found following repeated, whole-body or head-only exposures to continuous wave 900 MHz fields or to 900 and 1800 MHz GSM signals (Galloni et al, 2005a,b) or following head-only exposure to UMTS signals (Galloni et al, 2009). In addition, repeated, head-only exposure to continuous wave 900 MHz fields did not increase the ototoxicity induced by injection of the aminoglycoside antibiotic, gentamicin (Parazzini et al, 2007). However, the authors noted that the possibility of synergistic effects between other combinations of SARs or concentrations of antibiotic could not be excluded.

Budak and colleagues have investigated the effects of acute, daily exposure to 1800 MHz GSM signals on cochlear function in rabbits. Budak et al (2009a) reported that exposures of both young (1 month old) and adult female rabbits resulted in significant increases in the DPOAE of young animals, and significant decreases in the adults. Both changes were ascribed to increased temperatures in the ear canal. Significant increases in DPOAE were reported by Budak et al (2009b) in male rabbits exposed during late gestation and again at 1 month of age; prenatal exposure alone produced less extensive changes, while postnatal exposure alone produced significant decreases in DPOAE amplitudes. It was suggested that detrimental changes were confined to exposures of the young animals because the ear would have been protected by fluid during gestation; however, it is also possible that differences in SAR may help to explain these results, as the energy absorbed by the fetus would have been considerably less than that absorbed by the young animals. Lastly, it was suggested that exposure to 1800 MHz GSM signals produced less extensive decreases in DPOAE amplitudes in pregnant compared with non-pregnant rabbits (Budak et al, 2009c). This difference was ascribed to differing oestrogen and corticosteroid levels between groups. However, in none of these studies was any indication of the likely SAR in the animals given, which severely limits the interpretation of these results.

No significant effects on DPOAE were reported by Kayabasoglu et al (2011) following daily exposure of newborn or adult rats to mobile phone signals for 1 month. The study used a carousel system to expose the animals for 6 hours each day, but no further details were given, nor was a measure of SAR provided.

Kaprana et al (2011) reported that exposure to unmodulated 900 MHz signals at 0.2 W caused short-term changes in the auditory brainstem response of rabbits. Significant delays were seen in components of the auditory brainstem response ipsilateral to the exposed ear during exposure, but no effects were seen from the contralateral ear, or 24 hours after exposure. The SAR was not determined, and the possibility of localised thermal effects was acknowledged.

4.4.2 Summary

There is no compelling evidence that daily, repeated exposure to the fields associated with mobile phones has any detrimental effects on hearing in animals, either through changes to the inner ear or on the central auditory pathways. However, one group has reported changes in young rabbits, and other has reported acute changes in adult rabbits, both of which may be due to localised heating effects.

TABLE 4.10 Animal studies investigating effects on genotoxicity and mutagenicity

The SAR values are mean whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Vijayalaxmi et al, 2003	Micronuclei (MN) in 2000 polychromatic erythrocytes (PCE) in bone marrow of Fischer 344 rats, up to 9 days after exposure	1.6 GHz Iridium signals, for 2 h/day, 7 days/week from gestational day 19 until postnatal day 35, at 0.1–0.22 W kg^{-1} in brain, animals freely moving, and for 2 h/day, 5 days/week from day 35 to 2 years of age, at 0.16 or 1.6 W kg^{-1} in brain, head-only exposures, animals restrained	No significant increase in incidence	Mitomycin C (MMC, 0.01 mg kg^{-1}) caused significant increase, 24 h after injection Animals exposed with mothers until weaning (at 3 weeks of age) Animals part of carcinogenicity study (Anderson et al, 2004)
Vijayalaxmi et al, 2004	MN in 2000 PCE in peripheral blood or bone marrow of BALB/c mice, 24 h after exposure	42.2 GHz, pulsed at 60 Hz, for 30 min/day for 3 days at 622 W kg^{-1} (peak) in nose, animals restrained, and/or injected with cyclophosphamid (CCP, 15 mg kg^{-1}) on day 2 or 3	CCP significantly increased incidence of MN, no significant effect without CCP, and no significant interaction	Millimetre waves Exposure increased surface temperature of nose 1°C
Görlitz et al, 2005	MN in 2000 PCE in bone marrow (5 day) or peripheral blood (6 week) and 2000 keratinocytes from tail, and 1000 lymphocytes from spleen of B6C3F1 mice	902 MHz GSM or 1747 MHz DCS, for 2 h/day for 5 days at 3.3, 11 or 33 W kg^{-1}, or for 2 h/day for 5 days/week for 6 weeks at 2.8, 8.3 or 24.9 W kg^{-1}, animals restrained	No significant increase in any tissue at any SAR	Exposure consisted of 3 different 40 min phases emulating talking, listening and moving in environment Highest exposure did not increase body temperature Significant effects seen with CCP (30 mg kg^{-1}, orally)
Juutilainen et al, 2007	MN in 2000 PCE or normochromatic erythrocytes (NCE) in peripheral blood of: (a) CBA/S mice or (b) K2 transgenic and non-transgenic mice, 1–4 days after exposure	(a) 902 MHz NMT (CW) at 1.5 W kg^{-1}, or 902 MHz GSM at 0.35 W kg^{-1} for 1.5 h/day, 5 days/week for 78 weeks (b) 902 MHz GSM or 849 MHz D-AMPS, for 1.5 h/day, 5 days/week for 52 weeks at 0.5 W kg^{-1}, animals restrained	No significant increase in MN in PCE or NCE in (a) or (b)	Animals part of co-carcinogenicity studies with X-rays (Heikkinen et al, 2001) or ultraviolet radiation (Heikkinen et al, 2003)

Study	Model used	Exposure conditions	Results of exposure	Comments
Zieman et al, 2009	MN in 2000 PCE or NCE of peripheral blood of B6C3F1/Crl mice, 3–19 days after exposure	902 MHz GSM or 1747 MHz DCS, for 2 h/day for 5 days/week for 2 years, at 0.4, 1.3 or 4 W kg^{-1} (talking), animals restrained	No significant increase in MN frequency in PCE or NCE	Animals part of carcinogenicity study (Tillmann et al, 2007) Exposure consisted of 3 different 40 min phases emulating talking, listening and moving in environment MMC (1 mg kg^{-1}) caused significant increase, 48 h after injection
Gurbuz et al, 2010	MN in 1000 exfoliated bladder cells of Wistar rats	1800 MHz GSM, 20 min/day, 5 days/week for 4 weeks at 4.5 V m^{-1}, animals anaesthetised	No significant effects	SAR not given Using repeated anaesthesia seems unnecessary
Lagroye et al, 2004	DNA single strand breaks (SSB) in SD rat brain cells, using Olive and Singh versions of the alkaline comet assay, with and without proteinase K, 4 h after exposure	2.45 GHz, pulsed 2 µs, 500 pps, 2 h at 1.2 W kg^{-1}, animals confined within circular waveguide	No significant effects	Significant increases using 1 Gy gamma rays Did not confirm results of Lai and Singh, 1996
Belyaev et al, 2006	DNA double strand breaks (DSB) using pulsed-field gel electrophoresis, chromatin conformation using anomalous viscosity time dependencies, in Fisher 344 rat brain	915 MHz GSM, 2 h at 0.4 W kg^{-1}, animals confined in TEM cell	No significant effects	Modest changes in gene expression also seen
Verschaeve et al, 2006	DNA SSB in Wistar rat brain, liver and peripheral blood cells, using Singh version of the alkaline comet assay, MN in 1000 PCE	900 MHz GSM, for 2 h/day, 5 days/week for 24 months, at 0.3 or 0.9 W kg^{-1}, animals freely moving, and/or 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), (19 mg ml^{-1} in drinking water), all the time	No significant differences between combined treatment and MX alone	–

TABLE 4.10 *Continued*

Study	Model used	Exposure conditions	Results of exposure	Comments
Ono et al, 2004	Mutant frequency analysis of *lacZ* gene in spleen, liver, brain or testis of Muta™ mice, at 10 weeks of age compared with historical values	2.45 GHz, CW , 16 h/day on gestational day 0–15, intermittent exposure (10 s/min) at 0.71 W kg^{-1} (mean) 4.3 W kg^{-1} (peak), animals freely moving	No significant effects on mutant frequency or quality of mutation	Animals exposed in groups of 4 from 17:00 to 09:00 h Mean rectal temperature of dams raised by 0.4°C
Trosic et al, 2004a	PCE per 2000 erthyrocytes, MN in 1000 PCE in bone marrow cells of Wistar rats, after exposure	2.45 GHz, CW, 2 h/day for 2, 8, 15 or 30 days at 1.25 W kg^{-1}, animals confined	Significant increase in PCE on day 8 and 15, and in MN on day 15	Body temperature not increased by exposure
Demsia et al, 2004	MN in 1000 PCE in bone marrow cells of Wistar rats	910 MHz, 2 h/day for 30 days at 0.42 W kg^{-1} (peak), animals restrained	Significant increase, particularly in males	Not described in detail
Ferreira et al, 2006	MN in 1000 PCE in bone marrow cells of Wistar rats, on postnatal day 2	834 MHz, 8.5 h/day from gestational day 0 to birth, 26.8–40 V m^{-1} from phone, SAR of 0.55–1.23 W kg^{-1}	Significant increase in MN	Animals exposed from 17:30 to 02:00 h Also no significant effects on catalase, glutathione or other antioxidant functions in liver or blood
Kumar et al, 2010	MN in PCE in peripheral blood using flow cytometry	10 GHz at 0.014 W kg^{-1} or 50 GHz at 0.0008 W kg^{-1}, 2 h/day for 45 days, animals freely moving	PCE/NCE ratio significantly lower	Also significant decrease in glutathione peroxidise (GPx) and superoxide dismutase (SOD), and increase in catalase (CAT) activities and reactive oxygen species (but control values variable)
Paulraj and Behari, 2006	DNA SSB in Wistar rat brain cells using alkaline comet assay	2.45 GHz, at 1 W kg^{-1} or 16.5 GHz at 2.01 W kg^{-1} for 2 h/day, 5 days/week for 7 weeks, animals confined	Significant increase in length of DNA migration	–

Study	Model used	Exposure conditions	Results of exposure	Comments
Kesari et al, 2010a	DNA DSB in Wistar rat brain cells using alkaline comet assay	2.45 GHz, pulsed at 50 Hz, at 0.11 W kg^{-1} for 2 h/day, 5 days/week for 7 weeks, animals confined	Significant increase in comet head, tail length and tail movement	Also significant decreases in GPx, SOD and histone kinase, and increase in CAT activities
Lai and Singh, 2005	DNA SSB and DSB in SD rat brain cells using alkaline comet assay, 4 h after exposure	2.45 GHz, CW, 2 h at 0.6 W kg^{-1}, animals confined within circular waveguide, and/or 30–100 Hz magnetic field at 4.5 μT (noise)	CW alone significantly increased both SSB and DSB, no significant increases with noise alone or CW plus noise	Supports hypothesis of Litovitz and colleagues
Aitken et al, 2005	Alkaline and pulsed-field gel electrophoresis, and quantitative PCR of β-globin gene and a 10 kb fragment of mitochondrial DNA, in caudal epididymal sperm of CD1 mice	900 MHz, 12 h/day for 7 days at 0.09 W kg^{-1}, animals freely moving	No significant effects on SSB or DSB Significant decrease in both genes	No significant effects on sperm number, vitality or morphology. Animals exposed in groups of 4 or 5 from 19:00 to 07:00 h with food and water ad lib

TABLE 4.11 Animal studies investigating carcinogenic potential of RF fields alone in conventional strains

The SAR values are mean whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Anderson et al, 2004	Brain tumours in male and female Fisher 344 rats, by post-mortem pathology	1.6 GHz Iridium signals, 2 h/day from gestational day 19 until postnatal day 23 ± 2 (weaning), at 0.16 W kg^{-1} in brain, animals freely moving, and 2 h/day, 5 days/week from 35 ± 1 days old until 2 years of age, at 0.16 or 1.6 W kg^{-1} in brain, head-only exposure, animals restrained	No significant effects on early survival, weaning or growth weights, clinical signs, or incidence of brain tumours or other neoplasms	Significant increase in weight in male and female cage controls, and significant decrease in survival of female cage controls
Smith et al, 2007	Tumours in male and female Han Wistar rats, by post-mortem pathology	902 MHz GSM or 1747 MHz DCS, 2 h/day, 5 days/week for 2 years, at 0.4, 1.2 or 3.7 W kg^{-1} GSM, or 0.4, 1.3 or 4 W kg^{-1} DCS, animals restrained	Some incidental differences, but no significant effects on health status, clinical signs, food consumption, body or organ weights, or mortality No significant increase in numbers of tumour-bearing animals (TBA), total numbers of tumours (TNT), or in any specific tumour type	SAR of GSM reduced due to large rat growth Exposure consisted of 3 different 40 min phases emulating talking, listening and moving in environment Highest exposure below thermal threshold
Tillmann et al, 2007	Tumours in male and female B6C3F1 mice	902 MHz GSM or 1747 MHz DCS, 2 h/day, 5 days/week for 2 years, at 0.4, 1.3 or 4 W kg^{-1}, animals restrained	No significant effects on health status, clinical signs, food consumption, body or organ weights, or mortality No significant increase in numbers of TBA, TNT or in any specific tumour type	Sex-related differences Exposure consisted of 3 different 40 min phases emulating talking, listening and moving in environment Highest exposure below thermal threshold Incidence of all tumour types in line with historical values

Study	Model used	Exposure conditions	Results of exposure	Comments
Bartsch et al, 2010	Weight gain, survival, in female SD rats, tumour incidence by post-mortem pathology	900 MHz GSM, continuous exposure, except for 15 min/day (feeding), 4 x 1–2 h/week (health check and cleaning), 4–5 h/month (servicing) for up to 3 years of age, at 0.08 W kg^{-1} (young) to 0.038 W kg^{-1} (old), group of 12 animals freely moving in home cage	No significant effects with exposures < 2 years Significant reduction in median survival with exposures lasting > 2 years	Modest group sizes Effects on survival modulated by time of year of birth
Jin et al, 2011	Weight gain, survival, in SD rats, urinalysis, haematology, blood biochemistry after exposure, tumour incidence by post-mortem pathology	849 MHz CDMA or 1.95 GHz WCDMA, 45 min/day, 5 days/week for 1 year, at 2 W kg^{-1} (per signal), animals freely moving	No significant effects except significant increase in mean corpuscular haemoglobin level and alkaline phosphatase in males, and significant decrease in total bilirubin and lactate dehydrogenase in females	Exposures morning or afternoon alternately

TABLE 4.12 Animal studies investigating the potential of RF fields to promote tumours in tumour-prone animals

The SAR values are mean whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Sommer et al, 2004	Lymphoma in AKR/J mice, by post-mortem pathology, analysis of blood	900 MHz GSM, 24 h/day for 41 weeks, at 0.4 W kg^{-1}, in home cage, animals freely moving	No significant effects on survival, incidence of lymphoma and blood cell counts Significant increase in weight gain	Field turned off for 1 h twice per week for cleaning, animal inspection Results consistent with Oberto et al, 1997
Sommer et al, 2007	Lymphoma in AKR/J mice, by post-mortem pathology, analysis of blood	UMTS test signal, 1.966 GHz, 24 h/day for 35 weeks, at 0.4 W kg^{-1}, in home cage, animals freely moving	No significant effects on survival, incidence of lymphoma, lymphatic infiltrations, white blood cell counts and weight gain Lower weight in cage controls attributed to different feeding methods	Field turned off for 1 h twice per week for cleaning, animal inspection Results consistent with Oberto et al, 1997
Anghileri et al, 2005	Lymphoma in OF1 female mice by post-mortem pathology, up to 18 months of age	800 MHz, from mobile phone, 1 h each week for 4 months, animals freely moving	Decreased survival, earlier lymphocyte infiltration, formation of ascites and extra nodular tumours	Uninterpretable: absence of dosimetry, small numbers of animals and inadequate statistical analysis
Oberto et al, 2007	Lymphoma in *Pim1* transgenic mice, by post-mortem pathology, including animals at end of exposure	900 MHz, pulse width 0.577 ms, 217 Hz, 1 h/day for 18 months, at 0.5, 1.4 or 4 W kg^{-1}, animals restrained	Sporadic changes, but no consistent effects on clinical signs, weight gain, incidence of lymphoma, histiocystic sarcoma, or other tumours Survival decreased in all groups of males, and in females at 0.5 W kg^{-1}	Sex-related differences, and significant differences in cage control animals Does not confirm findings of Repacholi et al, 1997
Saran et al, 2007	Multiple tumours (medulloblastomas, rhadbomyosarcomas and preneoplastic lesions typical of basal cell carcinomas) in *Patched1 (Pct1)* heterozygous mice, by post-mortem pathology	900 MHz GSM, 2 x 30 min/day for 5 days, from postnatal day 2–6, at 0.4 W kg^{-1}, animals restrained in polystyrene jigs	No significant decrease in survival, no significant increase in incidence, onset or histology of tumours, or in preneoplastic skin lesions No effects on liver or other neoplasms	*Pct1* show peak sensitivity to X-rays during early postnatal life

TABLE 4.13 Animal studies investigating co-carcinogenic effects of RF fields with known carcinogenic agents

The SAR values are mean whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Shirai et al, 2005	CNS tumours in Fischer 344 rats, following transplacental ENU, by post-mortem histopathology	1.439 GHz TDMA signal, 90 min/day, 5 days/week from 5 weeks of age, for 104 weeks at 0.67 or 2 W kg^{-1} in brain, head-only exposure, animals restrained, and/or single maternal intravenous injection of ENU (4 mg kg^{-1}) on gestational day (dg) 18	No significant effects on CNS tumours, pituitary tumours significantly reduced in males at 2 W kg^{-1}, no significant effect on growth or survival	Carried out under good laboratory practice standards
Shirai et al, 2007	CNS tumours in Fischer 344 rats, following transplacental ENU, by post-mortem histopathology	1.95 GHz WCDMA signal, 90 min/day, 5 days/week from 5 weeks of age, for 104 weeks at 0.67 or 2 W kg^{-1} in brain, head-only exposure, animals restrained, and/or single maternal intravenous injection of ENU (4 mg kg^{-1}) on dg 18	No significant effects on CNS tumours, skin fibromas and large granular lymphocytic leukaemia significantly reduced in males exposed at 2 W kg^{-1}, no significant effect on growth or survival	Carried out under good laboratory practice standards
Zook and Simmens, 2006	Neurogenic tumours in SD rats, following transplacental ENU, by post-mortem histopathology, every 30 days between 171 and 325 days old	860 MHz pulsed, Motorola Integrated Radio Services signal, 6 h/day, 5 days/week (excluding holidays) from 50 days old, at 1 W kg^{-1} in brain, animals restrained, and/or single maternal intravenous injection of ENU (6.2 or 10 mg kg^{-1}) on dg 15	No significant effects on incidence, malignancy multiplicity or latency of spinal cord or spinal nerve tumours, cranial nerve tumours, or brain tumours	–

Study	Model used	Exposure conditions	Results of exposure	Comments
Tillmann et al, 2010	Tumours in B6C3F1 female mice, following transplacental ENU, by post-mortem histopathology	1.966 GHz UMTS, 20 h/day for up to 24 months starting on dg 6, at 4.8 or 48 W m^{-2}, peak SAR calculated at 5 W kg^{-1}, and/or single maternal intraperitoneal injection of ENU (40 mg kg^{-1}) on dg 14 in low exposure group, animals freely moving	No significant effects with UMTS alone Incidence, malignancy and multiplicity of lung carcinomas significantly increased in ENU+UMTS, and numbers of lung metastases (non-significantly) doubled	Thermal pre-study showed that the highest SAR did not induce measurable increase in temperature Significant effects on liver tumours seen, but discounted by authors due to possible confounding by *Helicobacter* infection
Heikkinen et al, 2006	Tumours in female Wister rats, with 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H) furanone (MX) throughout study, by extensive post-mortem histopathology	900 MHz GSM, 2 h/day, 5 days/week for 104 weeks, at 0.3 or 0.9 W kg^{-1}, animals freely moving, and MX (1.7 mg kg^{-1} in drinking water)	No significant effects on organ-specific incidence of any tumour type, effect in merged vascular tumours attributed to chance	Effects on genotoxic endpoints reported by Verschaeve et al, 2006
Yu et al, 2006	Mammary tumours in female SD rats, following single initiation with 7,12-dimethylbenz(a)anthracene (DMBA), by post-mortem histopathology	900 MHz GSM, 4 h/day, 5 days/week for 26 weeks at 0.44, 1.33 or 4 W kg^{-1}, animals restrained, and DMBA (35 mg kg^{-1}) by gavage	No significant effects on benign or malignant mammary tumours	Exposures began 1 day after DMBA treatment Significant differences in weight, tumour incidence and latency in cage controls
Hruby et al, 2008	Mammary tumours in female SD rats, following initiation with DMBA, by post-mortem histopathology	902 MHz GSM, 4 h/day, 5 days/week for 186 days at 0.44, 1.33 or 4 W kg^{-1}, animals restrained, and DMBA (17 mg kg^{-1}) by gavage	Sporadic significant differences observed, but no dose-related trends Overall, no differences attributed to exposure	Exposures began 1 day after DMBA treatment Significant differences in tumour incidence and malignancy in cage controls
Huang et al, 2005	Skin tumours in male ICR mice, following initiation with DMBA, by histopathology at sacrifice after 20 weeks	848.5 or 1762 MHz CDMA, 2 x 45 min/day, 5 days/week for 19 weeks, at 0.4 W kg^{-1}, animals freely moving, and DMBA (100 μg per 100 μl) painted on dorsal skin	No skin tumours, and no effects on epidermis	Exposures began 7 days after DMBA treatment, each 45-min exposure separated by 15 min Significant effects seen in positive control group (phorbol acetate)

TABLE 4.14 Animal studies investigating effects of RF fields on implanted tumour cells

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Radzievsky et al, 2004	B16 F10 melanoma cells injected subcutaneously (sc) into Swiss Webster mice	61.22 GHz, 15 min/day for 5 days at 133 W m^{-2} to the head, animals restrained	Significantly reduced tumour growth with exposures starting on day 5 after injection, no significant effects with exposures starting on day 1 or 10	Effect blocked by naloxone hydrobromide (1 mg kg^{-1}) Maximum temperature rise of around 1°C at tip of the nose
Logani et al, 2004	B16 F10 melanoma cells injected sc into SKH1 hairless mice, and/or intraperitoneal (ip) cyclophosphamide (30 or 20 mg kg^{-1}, CPA) on days 4–8	42.2 GHz, 60 Hz modulation, 30 min/day for 5 days at 365 W m^{-2} (peak) to the nose (peak SAR of 730 W kg^{-1}), animals restrained	Dose-dependent reduction in tumour growth with CPA, no additional effects with exposure on days 4–8 post-inoculation, nor with exposure before and/or after CPA	Temperature rise of 1.5°C on the nose
Logani et al, 2006	B16 F10 melanoma cells injected intravenously in female C57BL/6 mice on day 2 post-exposure, and/or CPA (150 mg kg^{-1}) ip; numbers of metastatic lung colonies counted after 2 weeks	42.2 GHz, 60 Hz modulation, 30 min at 365 W m^{-2} (peak) to the nose (peak SAR of 730 W kg^{-1}), animals anaesthetised	CPA alone significantly increased metastases, RF alone or RF+CPA significantly decreased metastases, RF+CPA significantly increased activity of natural killer cells	Temperature rise of 1.5°C on the nose

TABLE 4.15 Animal studies investigating effects of RF fields on the immune system and haematology

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Gatta et al, 2003	Spleen lymphocyte parameters in C57BL/6 mice, by ELISA, flow cytometry, immediately after exposure	900 MHz GSM, 2 h/day, for 1, 2 or 4 weeks, at 1 or 2 W kg^{-1}, animals restrained	No significant effects on total spleen cell counts or B- or T-cell frequency and proliferation, cytokine production, expression of activation markers	Transient increase in interferon-γ cytokine following exposure for 1 week
Nasta et al, 2006	Spleen B-cell maturation, antibody production, in female C57BL/6 mice, by ELISA, flow cytometry	900 MHz GSM, 2 h/day, 5 days/week for 4 weeks, at 2 W kg^{-1}, animals restrained	No significant effects on number or frequency of B-cells, or on antibody serum levels, induced antibody production, antigen-specific antibody response	Water cooling system used to ensure minimal heating during exposure
Prisco et al, 2008	Ability of bone marrow cells from female C57BL/6 mice 24 h after exposure to reconstitute the immune system of mice X-irradiated at 9 Gy	900 MHz GSM, 2 h/day, 5 days/week for 4 weeks, at 2 W kg^{-1}, animals restrained	All recipient mice survived for 6 weeks No significant effects on thymus or spleen T- and B-cell numbers, phenotype or proliferation 3 or 6 weeks after transplant	Water cooling system used to ensure minimal heating during exposure
Poulletier de Gannes et al, 2009b	Circulating antibodies (IgA, IgG and IgM) in Wistar rats, 7 and 14 days after exposure, by ELISA, teratology following maternal ip injection of blood serum (1 ml) taken 14 days after exposure on gestational day 10	2.45 GHz, CW, 7 h/day, 5 days/week for 6 weeks at 5 W m^{-2}, 0.16 W kg^{-1}, animals freely moving	No measurable effect on antibodies, no significant effects on numbers of implantations, resorptions or live fetuses, or on functional indices of pup development	Did not confirm early Soviet studies

TABLE 4.16 Animal studies investigating effects of RF fields on testicular function

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Ozguner et al, 2005	Histology and morphology of testes, hormone levels in SD rats, by microscopy and RIA	900 MHz, CW, 30 min/day, 5 days/week for 4 weeks, at 1 mW cm^{-2}, animals restrained	Diameter of seminiferous tubules and height of germinal epithelium significantly decreased without effect on spermatogenesis	Also, significant decrease in testosterone and non-significant decreases in luteinising or follicle-stimulating hormones
Ribeiro et al, 2007	Epididymal sperm count and testes morphology, in Wistar rats, using haemocytometer, image analysis	1835–1850 MHz GSM, 1 h/day for 11 weeks, at 4–14 W m^{-2}, from mobile phone in speech mode, animals freely moving in group of 8	No significant effects	Also, no effect of exposure on rectal temperature, circulating testosterone levels
Yan et al, 2007	Epididymal sperm count, motility and testes morphology, in SD rats, by microscopy, mRNA levels of cadherin-1 (CAD-1) and interstitial cell adhesion molecule 1 (ICAM-1) by RT-PCR, after exposure	1.9 GHz PCS, 2 x 3 h/day for 18 weeks, at 1.2–1.8 W kg^{-1}, head-mainly exposure, animals restrained	Sperm motility significantly decreased, and sperm stuck together in clumps, significant increase in CAD-1 and ICAM-1 No effect on morphology or total sperm number	30 min unrestrained rest between daily exposures No effect of exposure on rectal temperature
Daşdağ et al, 2008	Apoptosis in Wistar rats testes, using measurement of active caspase-3, by immunohistochemistry (IHC)	900 MHz GSM, 2h/day, for 10 months, at 0.07–0.57 W kg^{-1} in the testes, head-mainly exposures, animal restrained	No significant effects	Semi-quantitative scoring of protein expression
Yilmaz et al, 2008	Expression of bcl-2 protein in SD rat testes, by IHC	900 MHz GSM, 20 min/day for 30 days, at 0.52 W kg^{-1}, from mobile phone in speech mode, animals restrained	No significant effects	SAR varied during exposure between 0.29 and 0.87 W kg^{-1} Also, no significant effect in brain

TABLE 4.16 *Continued*

Study	Model used	Exposure conditions	Results of exposure	Comments
Mailankot et al, 2009	Epididymal sperm count and motility, in Wistar rats, using haemocytometer	900 or 1800 MHz GSM, 1 h/day for 28 days, from 'active mobile phone', animals freely moving in groups of 3	No effect on sperm count, but motility significantly reduced	No estimate of SAR Also, no effect of exposure on facial temperature, levels of glutathione and lipid peroxidation significantly reduced
Salama et al, 2009, 2010a	Ejaculated sperm count, motility and viability in New Zealand white rabbits, sampled twice per week during exposure, by microscopy, eosin-nigrosin and acridine orange tests, testes histopathology, and calorimetry for fructose	800 or 900 MHz GSM, 8 h/day for 12 weeks, at 0.43 W kg^{-1}, from mobile phone in standby mode, animals restrained	Significant decrease in sperm count and fructose level in semen after 8 weeks, sperm motility after 10 weeks, and seminiferous tubule diameter	SAR must be overestimation Also, no effect on circulating testosterone levels
Salama et al, 2010b	Copulatory behaviour in New Zealand white rabbits, 3 x 3 min mating per week for 2 weeks, after exposure	800 MHz GSM, 8 h/day for 12 weeks, at 0.43 W kg^{-1}, from mobile phone in standby mode, animals restrained	Significant decrease in ejaculation frequency, mount duration and frequency with ejaculation Significant increase in biting	SAR must be overestimation Also, no effect on circulating levels of testosterone, cortisol or dopamine. Appear to be same animals as used by Salama et al, 2009, 2010a
Otitoloju et al, 2010	Epididymal sperm head abnormalities in mice, by microscopy	Environmental exposure from GSM base stations, for 6 months, in 3 different locations	Incidence of abnormalities significantly increased, correlated with measured mean electric field strength (R^2 = 0.99)	Preliminary study only No apparent control of environmental factors at each site
Lee et al, 2010	Epididymal sperm count and cell cycle analysis, lipid peroxidation by MDA, apoptosis by TUNEL, p53, bcl-2, caspase-3, expression by IHC and immunoblotting, in SD rats testes	848.5 MHz CDMA, 2 x 45 min/day, 5 days/week for 12 weeks, at 2 W kg^{-1}, animals freely moving in reverberation chamber	No significant effects on any endpoint	Exposure periods separated by 15-min interval No effect of exposure on rectal temperature

Study	Model used	Exposure conditions	Results of exposure	Comments
Subbotina et al, 2006	Morphology of sperm in Wistar rats, by microscopy using H&E stain, every 7 days after exposure	Unspecified, within 30–300 GHz, for 30 min/day for up to 63 days, at 3 W m^{-2}	Abnormal sperm increased during exposure, from 35% on day 7, to 98% after 63 days	Very few experimental details, no statistical analysis
Kumar et al, 2011	ROS, cell cycle and histone kinase activity, by spectrophotometry and flow cytometry, in epididymal sperm of Wistar rats	10 GHz, CW, 2 h/day for 45 days, at 0.014 W kg^{-1}, animals freely moving	Significant increase in ROS and apoptosis Significant decrease in histone kinase and percentages of sperm in S and G_2/M phase	–
Kesari and Behari, 2010	GPx, SOD, catalase and histone kinase activity, and cell cycle by flow cytometry, in epididymal sperm of Wistar rats	50 GHz, CW, 2 h/day for 45 days, at 0.0008 W kg^{-1}, animals freely moving	GPx, SOD, histone kinase significantly decreased CAT significantly increased, apoptosis significantly increased Percentages of sperm in S and G_2/M phase significantly decreased	–

TABLE 4.17 Animal studies investigating effects of RF fields on pregnancy outcome and fetal development

The SAR values are whole-body averages, unless stated otherwise. Significant indicates statistically significant (usually at $p<0.05$)

Study	Model used	Exposure conditions	Results of exposure	Comments
Lee et al, 2009	Pregnancy outcome, visceral and skeletal abnormalities, external malformations, in ICR mice, on gestational day (dg) 18	849 MHz CDMA or 1.95 GHz WCDMA, 2 x 45 min/day on dg 1–17, at 2 W kg^{-1} (per signal), animals freely moving	No significant effects on mothers or offspring with CDMA or both signals	Exposure periods separated by 15-min interval All exposures not associated with temperature increase Some variability seen in sham-exposed groups
Ogawa et al, 2009	Pregnancy outcome, visceral and skeletal abnormalities, external malformations, in CD(SD) rats, on dg 20	1.9 GHz WCDMA, 90 min/day on dg 7–17, at 0.67 or 2 W kg^{-1} (in maternal brain), head-mainly exposure, animals restrained	No significant effects on mothers or offspring	All animals restrained for 90 min on dg 18–20 Whole-body SAR of fetus approximately half that of mother (<0.4 W kg^{-1})
Sommer et al, 2009	Fertility, pregnancy outcome, visceral and skeletal abnormalities, external malformations, reflex development in C57BL mice, over 4 generations	1.966 GHz UMTS, 23.5 h/day, at 1.35, 6.8 or 22 W m^{-2} (SARs of 0.08, 0.4 or 1.3 W kg^{-1}), animals freely moving, in groups of 2 or 3 adults, 2 adults and 6 pups, 4 young mice	No significant effects, except for trend towards lower food consumption in exposed males, few sporadic changes	SARs for 3 adult mice per exposure cage Second litter of each generation used due to infanticide
Takahashi et al, 2010	Fertility, pregnancy outcome, visceral and skeletal abnormalities, external malformations, growth, physical and reflex development, in Crl:CD(SD) rats Also behaviour of offspring in open field at 5 and 8 weeks, spatial memory in a water maze at 9 weeks, fertility and embryofetal losses in pregnant animals at 10 weeks	2.14 GHz WCDMA downlink signals, 20/day from dg 7 to postnatal day 21, at 0.028–0.040 or 0.066–0.093 W kg^{-1} in mothers, 0.029 or 0.068 W kg^{-1} in fetuses, 0.061–0.067 or 0.143–0.156 in offspring, animals freely moving	No significant effects on mothers or offspring, except time in target quadrant of water maze increased for males during probe trial	A few significant effects not considered to be of biological significance: pinna unfolding decreased on postnatal day 2, body weight of males increased 4–7 weeks after weaning, numbers of corpora lutea decreased, and body weights of live fetuses increased in lower exposure group

Study	Model used	Exposure conditions	Results of exposure	Comments
Sambucci et al, 2010	Pregnancy outcome, immunological function in C57BL/6 mice, using flow cytometry, ELISA at 5 and 26 weeks of age	2.45 GHz, pulsed Wi-Fi signal, 2 h/day, dg 5–19, at 4 W kg^{-1}, animals restrained	No consistent, significant effects on spleen cell number, B-cell frequency or antibody serum levels No effect of *in vitro* challenge with lipopolysaccharide on B-cell proliferation or production of IgM or IgG	Animals exposed using in different size jigs as pregnancy progressed
Contalbrigo et al, 2009	Plasma levels of glucose, triglycerides, total cholesterol, in SD rats, every 3 h, using portable glucometer, automated analyser	1800 MHz GSM, 19 h/day, from dg 12 until 56 weeks of age, at 25 or 50 V m^{-1}, animals freely moving in home cage	No significant effects	Study not amenable to interpretation: no description of exposure system, dosimetry lacking No measure of variability on data
Watilliaux et al, 2011	HSP60, HSP90, HSC70, serine racemase and glutamate transporters, GFAP expression using Western blot, morphology of microglial cells using immunohistochemistry (IHC), in brain of Wistar rats, 24 h after exposure	1800 MHz GSM, 2 h on postnatal day 5, 15, 35, at 0.13–1.2 W kg^{-1} (1.7–2.5 W kg^{-1} in brain), head-mainly exposure, animals anaesthetised	No significant effects in any brain region, at any age	Animal placed on heating pad during exposures
Gul et al, 2009	Morphology of ovarian follicles in (unspecified) rats, using microscopy, image analysis, at postnatal day 21	Unspecified signal from mobile phone beneath cage, in stand-by mode for 11 h 45 min and talk mode for 15 min per day, from dg 0 to birth, animals freely moving	Significant decreases in mean number of pups per litter, and in ovarian number and volume	Dosimetry lacking Phone battery charged continuously
Fragopoulou et al, 2010b	Skeletal anatomy in BALB/c mice, using Alcian Blue and Alizarin Red S, at birth and at 35 days	900 MHz GSM signal from a mobile phone in talk mode, 6 or 30 min/day from dg 0 to day 21, at 0.6–0.94 W kg^{-1}, animals freely moving in home cage	Delay in ossification in cranial bones and thoracic ribs No effect seen at 35 days	Females exposed to GSM signal for 6 or 30 min/day for 5 days immediately before pregnancy

TABLE 4.17 *Continued*

Study	Model used	Exposure conditions	Results of exposure	Comments
Pyrpasopoulou et al, 2004	Histology, expression of bone morphogenetic proteins (BMP-4, -7) receptor subunits (BMPR-IA, -IB, -II) in Wistar rat kidney, by microscopy, IHC, RT-PCR, at birth	9.4 GHz, pulsed length of 20 s and pulse rate of 50 Hz, continuously on dg 1–3 or 4–7, at 0.0005 W kg^{-1} (0.05 W m^{-2}) animals freely moving, in groups of 4	Significant changes in expression of BMP-4, BMPR-IA and BMPR-II, effects more pronounced on days 1–3	Signal scaled to rat dimensions in order to produce equivalent penetration as a GSM signal in man Paucity of exposure details
Odaci et al, 2008	Histology of the dentate gyrus in Wistar rat, using optical fractionator techniques, at 4 weeks of age	900 MHz, CW, 90 min/day from conception until birth, at 2 W kg^{-1} (peak), head-mainly exposure, animals restrained	Significant decrease in total number of granule cells	Data from 3 litters per treatment
Bas et al, 2009b	Histology of the area CA1 of the hippocampus in Wistar rat, using optical fractionator techniques, at 4 weeks of age	900 MHz, CW, 90 min/day from conception until birth, at 2 W kg^{-1} (peak), head-mainly exposure, animals restrained	Significant decrease in total number of pyramidal cells	Data from 3 litters per treatment
Rağbetli et al, 2009, 2010	Cell numbers, with H&E, cresyl violet, using automated counting system, in Swiss albino mouse brain on postnatal day 21	900 MHz GSM, at 1.2 or 0.95 W kg^{-1} from mobile phone, in standby mode for 11 h 45 min and talk mode for 15 min per day, from dg 1–20	Significant decrease in Purkinje cells in cerebellum, no effect on pyramidal cells in hippocampus	Dosimetric basis of reported SAR value unclear, only 5 or 6 animals per treatment group
Guler at al, 2010	MDA, 8-hydroxy-2'-deoxyguanosine (8-OHdG) in New Zealand white rabbit brain, by spectrophotometry, biochemical analysis, at birth	1800 MHz GSM, 15 min/day on dg 15–22, at 14 V m^{-1}, animals freely moving	No significant effects	Dosimetry lacking Mothers showed significant increase in MDA, 8-OHdG, not related to field status
Tomruk et al, 2010	MDA, 8-OHdG, ferrous oxidation in xylenol orange (FOX) in New Zealand White rabbit liver, by spectrophotometry, biochemical analysis, at birth	1800 MHz GSM, 15 min/day on dg 15–22, at 14 V m^{-1}, animals freely moving	No significant effects on MDA, 8-OHdG, FOX levels significantly decreased	Dosimetry lacking Comparable increases in MDA and FOX levels in exposed and non-exposed mothers and in non-pregnant exposed

Study	Model used	Exposure conditions	Results of exposure	Comments
Orendáčová et al, 2009	Bromodeoxyuridine (BrdU) uptake in parts of rostral migratory stream (RMS) of Wistar rat brains, by IHC, 24 h or 1–4 weeks after exposure	2.45 GHz pulsed: (a) 4 h/day for 2 days and (b) 8 h/day for 3 days, on postnatal day 7 or 24 months, at 28 W m^{-2}, animals freely moving in home cages	Day 7 exposed: significant increase on day 10, smaller increase at 3 and 4 weeks after (a), significant decrease on day 14, sustained decrease, 50% loss of body weight at 3 weeks after (b), 24-month exposed: no significant effects	Characteristics of field not given, SAR not determined and would vary between two ages Controls not sham-exposed Statistical analysis not complete
Orendáčová et al, 2010	Fos protein, nitric oxide (NO) in subventricular zone (SVZ) and RMS Wistar rat brains, by IHC and NADPH-diaphorase histochemistry, 2 h after exposure	2.45 GHz pulsed, 2 h on postnatal day 7 or 28, at 20–67 W m^{-2}, animals freely moving in home cages	Day 7 or 28 exposed: increase in Fos in SVZ, day 7 exposed: increase in NO in RM, day 28 exposed: decrease in NO in RMS	Characteristics of field not given, SAR not determined Controls not sham-exposed
Gagnon et al, 2003	Histology of thymus, adrenal, haematology, corridor behaviour, in Swiss Webster mice, at 21 days old	0–25 MHz broadband signals, 24 h/day from dg 18 to postnatal day 21, at 6.8 V (abstract says 12.8 V), animals freely moving in home cages	Increased numbers of animals with lesions, time to run corridor almost doubled	Paucity of field and exposure details and limited statistical analysis Changes in total white blood cell and absolute lymphocyte counts significantly elevated in both exposed and sham-exposed mothers
Gathiram et al, 2009	Fertility in male and female (unspecified) rats, by latency to parturition and analysis of litter	100 MHz – 3 GHz (Hivex Electromagnetic Field System-5), 8 h/day for 10 days, at 18 dB mV (peak), animals freely moving	No significant effects with exposure of either males or females, or males and females in pairs	Dosimetry lacking Hivex system used to treat HIV/AIDS

TABLE 6.1 Provocation studies assessing self-reported outcomes using mobile-phone-handset-type exposures

Study	Sample	Type of exposure	Number and length of exposures	Type of self-report symptoms measured *Significant differences between RF and sham conditions show in italics*
Cinel et al, 2008	496 controls	888 MHz GSM, CW	Two 40-min exposures per participant: one either GSM or CW, and one sham	Headache, dizziness, fatigue, itching or tingling on skin, sensation of warmth on skin
Curcio et al, 2005	20 controls	902 MHz GSM	Two 45-min exposures per participant: one GSM and one sham	Sleepiness
Curcio et al, 2009	11 controls	902 MHz GSM	Two 40-min exposures: one GSM and one sham	Energy, fatigue, tension, difficulty concentrating, tingling of skin, dizziness, redness of ears, sensations of warmth on skin, pain, ***headache (greater headache during the sham condition)***
Hillert et al, 2008	38 sensitive people 33 controls	884 MHz GSM	Two 2¾ h exposures: one GSM and one sham	Headache (control group: ***more headache in the RF condition)***, fatigue, nausea, vertigo, difficulty concentrating, feeling low spirited, vision problems, dermal complaints, stress, ear heat ***(higher scores for both groups in RF condition)***, ear pain, sleepiness, arousal, other
Hung et al, 2007	10 controls	900 MHz GSM, in 'talk,' 'listen' and 'standby' modes	Four 30-min exposure to each of the three GSM modes and to a sham condition	Sleepiness
Johansson et al, 2007	15 people with atopic dermatitis 15 controls	900 MHz GSM	Two 30-min exposures: one GSM and one sham	'Symptoms perceived during or after the provocation' No statistical analysis of the symptom data was attempted by the authors
Kleinlogel et al, 2008	15 controls	1950 MHz 'weak' UMTS, 1950 MHz 'high' UMTS) and 900 MHz GSM	Four 30-min exposures per participant; one weak UMTS, one high UMTS, one GSM and one sham	General discomfort, current disposition

Study	Sample	Type of exposure	Number and length of exposures	Type of self-report symptoms measured *Significant differences between RF and sham conditions show in italics*
Koivisto et al, 2001	96 controls	902 MHz GSM	Two 60-min exposures ($n = 48$) or two 30-min exposures ($n = 48$): one GSM and one sham	Headache, dizziness, fatigue, itching or tingling of the skin, redness of the skin, sensations of warmth on the skin
Nam et al, 2009	18 sensitive people 19 controls	835 MHz CDMA	Two 30-min exposures: one CDMA and one sham	Redness, itching, warmth, fatigue, headache, dizziness, nausea, palpitation, indigestion
Nieto-Hernandez et al, 2011	60 sensitive people 60 controls	385 MHz TETRA, CW	Three 50-min exposures per participant: one TETRA, one CW and one sham	Positive mood, negative mood, headache, fatigue, 'difficulty concentrating or thinking,' 'feeling irritable, anxious or depressed,' nausea, dizziness, sensations of warmth or burning, ***itching*** Sensations of itching showed a significant decrease in the sensitive group in the CW condition
Oftedal et al, 2007	17 sensitive people	902.4 MHz GSM	Up to eight 30-min trials per participant: four RF and four sham for most participants	Headache, 'any other symptoms' affecting the head
Riddervold et al, 2010	53 controls	420 MHz TETRA	Two 45-min exposure: one TETRA and one sham	Perceived air temperature, air humidity, air quality, sweating, freezing, breathlessness, tingling, pain, sleepiness, nausea, dizziness, headache, concentration difficulties
Rubin et al, 2006	69 sensitive people 60 controls	900 MHz GSM, CW	Three 50-min exposures per participant: one GSM, one CW and one sham	Headaches, nausea, fatigue, dizziness, itching or tingling or stinging of the skin, warmth or burning on skin, eye pain or dryness, 'severe reaction'
Wilen et al, 2006	20 sensitive people 20 controls	900 MHz GSM	Two 30-min exposures: one GSM and one sham	Whether the participant reported any symptoms during or after the experiment

TABLE 6.2 Provocation studies assessing self-reported outcomes using mobile-phone-base-station-type exposures

Study	Sample	Type of exposure	Number and length of exposures	Type of self-report symptoms measured *Significant differences between RF and sham conditions show in italics*
Augner et al, 2009	8 sensitive people 49 controls	900 MHz GSM, 'low', 'medium' or 'high' strength	Five 50-min exposures, separated by 5-min breaks	Good mood, alertness and calmness ***Participants who received higher levels of exposure were significantly more calm than participants who received lower levels of exposure***
Danker-Hopfe et al, 2010	397 controls	900 and 1800 MHz GSM (combined)	Ten nights of exposure, each randomly allocated to real or sham exposure	Subjective sleep efficiency, restfulness in the morning, time in bed, total sleep time, sleep onset latency and wake after sleep onset
Eltiti et al, 2007	44 sensitive people 114 controls	900 and 1800 MHz GSM (combined) and UMTS	Three 50-min exposures: one to GSM, one to UMTS and one to sham. Plus three 5-min exposures, one to each condition	Anxiety, tension, ***agitation (sensitive: UMTS resulted in higher agitation than sham)***, relaxation, discomfort, tiredness, plus overall symptom severity and occurrence for a list of 57 symptoms
Fritzer et al, 2007	20 controls	900 MHz GSM	Six night-long exposures (n = 10) or sham (n = 10)	Well-being, sleep quality
Furubayashi et al, 2009	11 sensitive people 43 controls	2.14 GHz WCDMA continuous exposure and intermittent exposure with signal randomly turned on and off every 5 min	Four 30-min exposures: two active, one sham, and one sham with noise as a stressor	Tension, depression, anger, vigour, fatigue, confusion, discomfort

Study	Sample	Type of exposure	Number and length of exposures	Type of self-report symptoms measured *Significant differences between RF and sham conditions show in italics*
Leitgeb et al, 2008	43 sensitive people	Faraday cage of electric conductive material mounted around the participant's own bed at home	Nine nights of sleep: three under genuine protective material, three under sham material, and three under no material	Sleep quality, awakening quality, sleep efficiency, overall sleep score Three participants showed results indicating significant ($p < 0.05$) improvements in total sleep score in the genuine protective condition compared to the other two conditions, as well as significant improvements in sleep quality ($n = 1$), awakening quality ($n = 1$) or sleep efficiency ($n = 1$). However, subsequent checks revealed that all three participants appeared to have unblinded the study
Regel et al, 2006	33 sensitive people 84 controls	1 or 10 V m^{-1} UMTS	Three 45-min exposures: one each to strong, weak or sham exposure	Tenseness, apprehension, worry, anxiety, being sceptical, unease, anxiety, somatic symptoms, inadequacy, depression, hostility
Riddervold et al, 2008	40 control adults 40 control adolescents	2140 MHz UMTS, 2140 MHz UMTS lacking some control features, and CW	Four 45-min exposures: one to each active exposure and one sham exposure	Perceived air temperature, air humidity, air quality, sweating, chilling, breathlessness, tingling, pain, sleepiness, nausea, dizziness, ***headache, concentration difficulties (both differences may reflect higher baseline levels in the sham condition)***
Wallace et al, 2010	48 sensitive people 132 controls	420 MHz TETRA	Four 5-min exposure: two sham and two TETRA Two 50-min exposures: one sham and one TETRA	Severity of anxiety, tension, arousal, relaxation, discomfort and tiredness, and how many out of 57 other symptoms that were reported

TABLE 6.3 Provocation studies assessing RF field perception among participants who report sensitivity to electromagnetic fields

Study	Sample	Type of exposure	Number and length of exposures	Total number of correct discriminations between conditions
Bamiou et al, 2008	9 sensitive people 21 controls	882 MHz GSM handset and CW	Six 30-min exposures: two GSM, two CW and two sham	77/180 (43%) There was no significant difference in the mean number of correct guesses between sensitive and controls No participants were correct in all six sessions
Barth et al, 2000	1 sensitive person	Mobile phone	Patient exposed to 15 active provocations and 16 inactive provocations	Sensitive: 13/31 (42%)
Eltiti et al, 2007a	44 sensitive people 114 controls	900 and 1800 MHz GSM (combined) and UMTS	Three 50-min exposures: one GSM, one UMTS and one sham; plus three 5-min exposures, one to each condition	Sensitive: 73/132 (55.2%, 5-min exposures) and 79/132 (59.8%, 50-min exposures) Control: 176/342 (51.4%, 5-min exposures) and 171/342 (50.1%, 50-min exposures) Two sensitive and five control participants were able to correctly identify all six conditions
Furubayashi et al, 2009	11 sensitive people 43 controls	2.14 GHz WCDMA base station continuous exposure and intermittent exposure with signal randomly turned on and off every 5 min	Four 30-min exposures: two active, one sham, and one sham with noise as a stressor	Sensitive: 34/66 (52%) Control: 126/258 (49%)
Hillert et al, 2008	38 sensitive people 33 controls	884 MHz GSM handset	Two 2¾ hr exposures: one GSM and one sham	Sensitive: 26/75 (35%) Control: 21/62 (34%)

Study	Sample	Type of exposure	Number and length of exposures	Total number of correct discriminations between conditions
Kwon et al, 2008	6 sensitive people 78 controls	902 MHz GSM handset	Minimum of 600 trials per participant of RF or sham stimulus Each condition lasted for 5 s	Mean correct response rate for sensitive (n = 6, 100 'on/off' trials) = 47% and for most controls (n = 76, 100 'on/off' trials) = 51% No sensitive and two control participants initially showed 'extraordinary' performance in discriminating active from sham – they were subsequently unable to replicate this performance
Nam et al, 2009	18 sensitive people 19 controls	835 MHz CDMA handset	Two 30-min exposures: one CDMA and one sham	Sensitive: accuracy for exposure = 43.3%, accuracy for non-exposure = 73.9% Control: accuracy for exposure = 3.2%, accuracy for non-exposure = 95.1% Significant differences ($p < 0.01$) between groups for both exposure types, attributable to the increased tendency of the sensitive group to report having detected a signal, regardless of the experimental conditions
Nieto-Hernandez et al, 2011	60 sensitive people 60 controls	TETRA handset and CW	Three 50-min exposures per participant: one TETRA, one CW and one sham	Sensitive: 104/180 (58%) Control: 108/180 (60%)
Oftedal et al, 2007	17 sensitive people	902.4 MHz GSM handset	Up to eight 30-min trials per participant: four RF and four sham for most participants	Sensitive: 52/129 (40%)
Raczek et al, 2000	16 sensitive people	900 MHz GSM	Series of 21 trials, each consisting of three 3-min exposures: one active and two inactive	Sensitive: 94/336 (28%) None of the participants met the threshold for being able to discriminate active from sham
Radon et al, 1998	11 sensitive people	900 MHz GSM	Series of 12 trials, each consisting of three 2-min exposures: one active and two inactive	Sensitive: 15/132 (11%) None of the participants met the threshold for being able to discriminate active from sham

TABLE 6.3 ***Continued***

Study	Sample	Type of exposure	Number and length of exposures	Total number of correct discriminations between conditions
Regel et al, 2006	33 sensitive people 84 controls	1 or 10 V m^{-1} UMTS base station exposure	Three 45-min exposures: one each to strong, weak or sham exposure	Sensitive: 17/31 (55%) Control: 22/57 (47%)
Rubin et al, 2006	69 sensitive people 60 controls	900 MHz GSM handset and CW	Three 50-min exposures per participant: one GSM, one CW and one sham	Sensitive: 110/192 (57%) Control: 96/180 (53%)
Wallace et al, 2010	48 sensitive people 132 controls	420 MHz TETRA	Four 5-min exposure: two sham and two TETRA Two 50-min exposures: one sham and one TETRA	Sensitive: 148/296 (50.0%) Control: 378/792 (47.7%) Two sensitive and three control participants were able to correctly identify all six conditions

TABLE 8.1 Epidemiological studies of lymphatic and haematopoietic cancer in people potentially exposed to RF fields through work or hobbies

Study	Type of study	Study population	Exposure condition	Disease outcome	Number of exposed cases	Estimated relative risk (with 95% CI)
Berg et al, 2006	Case–control	General population in Germany	Self-reported occupational activity	Brain tumours	38 glioma 26 meningioma	1.04 (0.68–1.61) 1.12 (0.66–1.87)
Karipidis et al, 2007	Case–control	General population in Australia	Self-reported occupation and job-exposure matrix	Non-Hodgkin's lymphoma	16	1.82 (0.79–4.16)
Degrave et al, 2009	Cohort	Belgian military	Military service in radar battalion	Cause-specific mortality	424 all-cause 133 cancer	1.04 (0.96–1.14) 1.23 (1.03–1.47)

TABLE 8.4 Case–control studies of mobile phone use and risk of brain tumours

Study	Country	Tumour type	Number of cases	Number of controls	Age at diagnosis (years)	Source of controls	Prevalence of ever-use in controls	Odds ratios (95% CI) ever-use
Hardell et al studies								
Hardell et al, 2005c, 2006c	Sweden	Malignant tumours	317	692	20–80	Population register	51%	2.6 (1.5–4.3) analogue 1.9 (1.3–2.7) digital
		Meningioma	413 benign					1.7 (0.97–3.0) analogue 1.3 (0.9–1.9) digital
		Acoustic neuroma						4.2 (1.8–10) analogue 2.0 (1.05–3.8) digital
Hardell et al, 2010	Sweden	Malignant tumours, deceased	346	619 deceased	20–80	Cause of death register	24%	1.7 (1.1–2.7) analogue 1.4 (0.97–2.1) digital 1.3 (0.9–1.9) mobile phone
Hardell et al, 2006a,b,d; Mild et al, 2007; Hardell and Carlberg, 2009 (pooled studies)	Sweden	Malignant tumours	905	2162	20–80	Population register	?	1.5 (1.1–1.9) analogue 1.3 (1.1–1.6) digital
		Meningioma	1254 benign					1.3 (0.99–1.7) analogue 1.1 (0.9–1.3) digital
		Acoustic neuroma						2.9 (2.0–4.3) analogue 1.5 (1.1–2.1) digital
Interphone studies: individual country analyses								
Christensen et al, 2004, 2005	Denmark	Glioma	252	822*	20–69	Population register	47%	0.7 (0.5–1.0)
		Meningioma	175					0.8 (0.5–1.3)
		Acoustic neuroma	106	212			46%	0.9 (0.5–1.6)

TABLE 8.4 *Continued*

Study	Country	Tumour type	Number of cases	Number of controls	Age at diagnosis (years)	Source of controls	Prevalence of ever-use in controls	Odds ratios (95% CI) ever-use
Lönn et al, 2004a, 2005	Sweden	Glioma	371	674	20–69	Population register	59%	0.8 (0.6–1.0)
		Meningioma	273	674				0.7 (0.5–0.9)
		Acoustic neuroma	148	604				1.0 (0.6–1.5)
Hepworth et al, 2006	UK	Glioma	966	1716	18–69 (northern) 18–59 (southern)	GP lists	52%	0.9 (0.8–1.1)
Schüz et al, 2006a; Schlehofer et al, 2007	Germany	Glioma	366	732	30–69	Population register	35%	1.0 (0.7–1.3)
		Meningioma	381	762			–	0.8 (0.6–1.1)
		Acoustic neuroma	97	194			38%	0.7 (0.4–1.2)
Klaeboe et al, 2007	Norway	Glioma	289	358	19–69	Population register	63%	0.6 (0.4–0.9)
		Meningioma	207					0.8 (0.5–1.1)
		Acoustic neuroma	45					0.5 (0.2–1.0)
Hours et al, 2007	France	Glioma	96	96	30–59	Electoral rolls	56%	1.1 (0.6–2.0)
		Meningioma	145	145			55%	0.7 (0.4–1.3)
		Acoustic neuroma	109	214			53%	0.9 (0.5–1.6)
Takebayashi et al, 2007	Japan	Glioma	88	163	30–69	General population fixed-line phone numbers	57%	1.2 (0.6–2.4)
		Meningioma	132	229			–	0.7 (0.4–1.2)
		Acoustic neuroma	97	330			31%	0.7 (0.4–1.2)

Study	Country	Tumour type	Number of cases	Number of controls	Age at diagnosis (years)	Source of controls	Prevalence of ever-use in controls	Odds ratios (95% CI) ever-use
Interphone studies: pooled analyses								
Lahkola et al, 2007, 2008	Denmark, Finland, Norway, Sweden, UK (southern)	Glioma	1521	3301	18–69	Population registers (D, F, N and S) or GP lists (UK)	59%	0.8 (0.7–0.9)
		Meningioma	1209	3299			58%	0.8 (0.6–0.9)
Schoemaker et al, 2005	Denmark, Finland, Norway, Sweden, UK	Acoustic neuroma	678	3553	–	Population registers (D, F, N and S) or GP lists (UK)	54%	0.9 (0.7–1.1)
Interphone Study Group, 2010, 2011	13 countries	Glioma	2708	2972	30–59	Population registers, electoral rolls, GP lists, random digital dialling, health ministry client register	64%	0.8 (0.7–0.9)
		Meningioma	2409	2662			56%	0.8 (0.7–0.9)
		Acoustic neuroma	1105	2145			61%	0.8 (0.7–1.0)
Studies of tumours in children								
Aydin et al, 2011	Denmark, Norway, Sweden, Switzerland	Brain	352	646	7–19	Population registers	51%	1.36 (0.92–2.02) regular use
							13%	1.26 (0.70–2.28) ≥5 years use

• But 801 in most tables.