Section 6

Biological Effects of Radiofrequency Field Exposure

Section 6B Animal Studies

Table of Contents

Summary

- Studies using animals have historically proven useful for investigating health effects; a large number of such studies have recently been conducted (2005–2012) to evaluate whether exposure to radiofrequency (RF) fields has adverse biological effects.
- Long-term bioassays, designed to determine whether RF exposure either alone or in conjunction with known mutagens can initiate or promote development of cancer in animals, have been uniformly negative.
- Studies of RF fields and toxicological effects such as DNA damage, micronucleus formation, apoptosis, reactive oxygen species, and gene expression changes have been inconsistent and the results contradictory. Positive studies have proven difficult to replicate. This lack of consistency reduces the likelihood that exposure to RF fields has toxicological effects in animals.
- There is no consistent evidence that exposure to RF fields produces biological effects in animal central nervous systems. Most recent investigations have been unable to confirm Swedish studies suggesting that RF exposure alters blood-brain barrier permeability; however, other aspects of brain physiology are less well studied. Behavioural investigations of the role of RF exposure on animal learning and cognitive function are mixed, with most being negative.
- Immune function studies have been mostly negative, although most of the studies to date have been conducted in adult animals. Earlier Soviet study results, indicating that serum taken from RF-exposed animals could increase embryo mortality when injected intraperitoneally into pregnant rats, have not been confirmed. Notwithstanding this, more studies are needed on RF effects in young animals.
- Effects of RF exposure on endocrine function, particularly on melatonin levels, have been negative, and studies of their effect on reproductive function in female animals have also been negative.
- Overall, studies have not shown convincing evidence that RF field exposure produces adverse biologic effects in animals. There are many negative results, and the relatively few positive results are rarely replicated in confirmatory studies. Most of the recent studies are characterized by good research protocols including appropriate control of thermal effects and excellent animal care along with appropriate use of reverberation chambers to ensure uniform specific absorption rates (SAR) in whole body RF dosimetry, or of animal restraints in the case of RF fields applied to specific organs such as the brain. These recent studies have generally shown no association of specific outcomes with exposure to RF.
- There is no recognized biologic mechanism by which RF exposure might operate to cause adverse biological effects in animals.

6B.1 Introduction

The use of animal models is common in testing for potential adverse (or beneficial) effects of exposure to a variety of agents in the environment. These agents include forms of non-ionizing radiation such as ultraviolet (UV) light and RF fields. Animals carry many genes analogous to those in humans, and have similarities in embryogenesis, development, and other physiological processes which could help predict possible biological effects in man. Unlike experiments carried out in isolated cell cultures, use of animal models allows for study of the physiological interactions which take place in living systems.

Research using animals is conducted using several animal types; the most common being rats and mice. While different anatomically and physiologically from humans, and with a much shorter lifespan, other aspects of their physiology, such as their DNA repair mechanisms, are very similar to those in humans. Barring differences resulting from species-specific sensitivity to the effects of a particular exposure, animal testing can reveal biologic effects which are very relevant to humans.

The nature of the putative effect to be studied sometimes dictates which type of animal is selected for a study. Long-term bioassays—used to study carcinogenesis and discussed below—normally use outbred or hybrid strains of rodents, as their genetic diversity closely mimics human diversity. Some studies are carried out in animal models that demonstrate a predisposition to a disease as a result of genetic alterations or exposure to a specific chemical or physical agent that initiates or accelerates the disease process. Use of animals for studies must also take into consideration the nature of the effects a particular agent may have on the animal over and above the effect being tested. One of the issues of significant importance to the study of the effects of RF fields is that, like all microwaves, the fields may have a local heating effect, particularly in small animals. Increased core heating by as little as 1˚C is known to affect several aspects of physiology.[1] Humans are much bigger than lab animals, and consequently any potential local heating effect might be diffused more quickly, and be less likely to affect physiology. Further, the power levels of RF devices in common use and of most human concern such as mobile phones generate specific absorption rates (SAR) within the human body which are too low to generate any thermal effects. Animal testing which focuses on the non-thermal effects from energy deposition due to day-to-day use of RF-emitting devices may be of relevance to human disease.

In order to avoid potential localized heating generated by RF fields, investigators in recent animal studies have evolved specialized laboratory devices such as rotating carousels and anechoic or reverberation chambers to improve control and uniformity of RF dosimetry in small animals. Examples of this include a rotating “ferris wheel” exposure instrument mechanism[2] or the carousel proposed as by Kuster and colleagues (2006).[3] Such devices have given more recent studies better control over thermal effects, and equally importantly, more precision in the actual RF dose

administered. Specialized exposure vessels such as anechoic and reverberation chambers, allow animals freedom of movement and hence allow exposure to low levels of RF fields for much longer periods of time—much like those seen in human activity. However, animal exposures in such chambers are "whole body" and cannot be restricted to specific organs such as the brain alone. For more precise measurement of exposure devices such as polycarbonate "capsules" are used in which small animals are placed to restrain them in position in order to help attain precise SAR in small organs such as the brain. These devices have been found to reduce animal distress during exposure, which is valuable from a humane perspective, but also act to reduce stress-related physiologic effects which might confound study results. However, use of restraints also restricts the amount of time that animals can be exposed to RF fields.

While use of the technologic advances such as those described above is more common in recent studies, some investigations used crude techniques such as a mobile phone placed in the cage as a RF field source. The resulting exposure to individual animals, and especially to specific organs, is ill-defined and cannot meet current RF dosimetry standards essential to proper interpretation of experimental results.[3]

6B.2 Purpose

The objective of the section is to summarize the state of knowledge from animal studies concerning possible adverse health effects of RF fields. The intent is to focus specifically on research conducted from around 2005–2006 in order to take advantage of the improved study protocols and RF exposure technology incorporated into recent studies.

6B.3 Methods

A search of the online databases PubMed (MEDLINE) and EBSCO Academic Search was conducted using search terms "radiofrequency field," "radiofrequency radiation," "RF radiation," "microwave," "cellular phone," and "mobile phone," and these terms were combined with terms for cancer, carcinogenesis, DNA damage, apoptosis, gene expression, reactive oxygen species, protein expression, blood-brain-barrier permeability, brain physiology, central nervous system effects, immune function, endocrine function, and female reproductive function. The search was restricted to peer-reviewed articles published in English, during the period 1990–2011, and then a filter was applied to identify studies conducted in animals, reducing these to 380 after elimination of duplicates. Restricting studies to those published since 2005 and eliminating duplicate references picked up in more than one search reduced the number to 142 for more detailed review. A separate search using the term "WiFi" linked to cancer, and various other terms including "health," produced only two animal investigations. Review articles were separated out so bibliographies could be searched; and recent national reviews of RF fields and health such as the Latin American Experts Committee on High Frequency Electromagnetic Fields and Human Health report (2010)[4]

and the UK Health Protection Agency's recent report (2012)[5] were also examined for papers missed by other means.

This review concentrates mainly on more recent studies (2005–2011), although summary paragraphs at the end of each group of potential adverse biological effects will consider all available evidence and not just studies conducted since 2005. The reason for the emphasis on more recent work is that these investigations are more likely to be characterized by good RF dosimetry and better control of the potential confounding effects of thermal changes due to RF exposure. Sometimes, investigations conducted many years ago will be referenced to provide context for study of a particular possible adverse effect. For example, several studies conducted in the Soviet Union in the 1980s are referenced as their reported biologic effects provided the impetus for recent (2009–2010) investigations. Tabular data will similarly emphasize recent studies rather than older ones published prior to 2005. Due to their high cost and long duration, animal carcinogenesis bioassays are relatively uncommon, so key studies back to 1992 will be considered.

Major categories of potential adverse biologic effects (cancer, neurologic function, immune effects, etc.) will be discussed. Within each category, a representative group of studies has been chosen for tabular presentation and discussion. These studies are, for the most part, characterized by good descriptions of RF dosimetry, use of RF frequencies that humans are exposed to on a day-to-day basis (such as Global System for Mobile Communication [GSM] and Code Division Multiple Access [CDMA] mobile phone frequencies), appropriate use of animal restraints and exposure system technology to ensure accurate organ-specific or whole body SAR values, and maximum SAR values of around 2 W/kg. On occasion, findings which may not satisfy these selection criteria but have been influential in public or scientific discussions of RF and health are also included.

6B.4 Cancer and RF Exposure

Perhaps the single greatest long-term public concern with use of RF wireless technology is whether it has the ability to initiate or promote the development of cancer. In general, carcinogenesis studies are grouped into the following categories:

1. Long-term two-year bioassays performed to detect increased incidence of spontaneous malignancies in outbred animals

2. Studies on tumour-prone animals designed to determine whether RF exposure alone increases the incidence of specific cancers

3. Studies to determine whether RF exposure increases the incidence of specific cancers initiated by known carcinogens such as dimethylbenz(a)anthracene (DMBA) or prenatal N-ethyl-N-nitrosourea (EMU).

A number of high quality studies have been conducted on each of these topics.

The first group, long-term bioassays, are studies of up to two years in duration, which are conducted in mice or rats. The studies follow very well defined criteria, with animals exposed to a test agent for relatively long periods of time. Animal group sizes are large and study designs usually include histopathologic evaluation (a microscopic examination to detect abnormalities at the cellular level) of samples of forty or more different tissues per animal. Exposure to the chemical or agent of interest commonly begins when animals are young and continues for up to two years. Bioassays (and most animal studies) include a so-called sham group which serves as a control group. These animals are exposed to all the same conditions that the other experimental animals except for the RF field. This helps to ensure that any adverse effects seen in the exposed animals are due to the RF exposure itself and not to other factors such as diet, confinement, stress, etc.

Independent analyses by the International Agency for Research on Cancer and the U.S. National Toxicology Program have shown in general that results of the two-year bioassays in rodents have a high predictive value for cancer in humans. These studies are commonly accepted by regulatory agencies as providing the most complete assessment of carcinogenicity,[6] the process by which normal cells become cancerous.

6B.4.1 Cancer and RF exposure – long- term bioassays (Table 1)

Chou and colleagues (1992)[7] exposed 200 Sprague-Dawley rats to 2450 MHz pulsed signal at SARs of 0.4 W/kg for a 200 gram animal to 0.15 W/kg for an animal weighing 800 grams, or sham for 21.5 hours per day, 7 days per week for a period of 25 months in order to determine whether two years of exposure altered the incidence of cancer in the animals compared to controls. The exposure began at eight weeks of life. All animals were histopathologically examined as they died during the course of the study, and at 25 months all surviving rats were euthanized and had a complete examination. No significant differences were seen between RF-exposed animals and the control rats for tumour incidence at any site.

A further study by La Regina et al. (2003)[8] involved exposing 80 male and 80 female Fischer rats to either 835 MHz FDMA or 847 MHz CDMA modulated RF fields for four hours a day, five days per week for two years in individual restraining devices within insulated exposure chambers. The authors reported that by the end of the first few days of the study, rats became familiar with the restraint process and most were sleeping at the end of each RF exposure. No indications of stress were reported by the investigators. Time-averaged SAR in the brain tissue of the exposed rats was about 0.85 W/kg. A third group of 80 male and 80 female rats underwent sham exposure under the same conditions. At the end of the study, surviving rats were killed and necropsied, and all data on these rats and those dying during the course of the study were analysed. The number and type of tumours were compared for each of the RF-exposed groups to that seen in the sham rats. No significant differences in malignant or benign tumours at any anatomic site were seen between RF-exposed and sham-

exposed rats. No significant differences were seen between groups in body weight or overall health.

Anderson et al. (2004)[9] obtained three sets of 36 pregnant Fischer 344 rats and exposed them to a 1600 MHz signal at 19 days of gestation for two hours per day, five days per week. Exposure of their 700 pups continued to 23 days after parturition. From these pups, 90 males and 90 females were assigned to each of three groups. One was exposed at 1.6 W/kg a second at 0.16 W/kg, and the third group became sham controls. An additional 80 male and 80 female pups served as cage controls—animals which are not exposed to either the RF fields or to the physical conditions of the exposed and sham-exposed animals. Near field RF of two hours per day, five days per week was continued in the exposed groups until the rats were two years old. At the end of the study, no significant differences were seen in cancers between the RF-exposed and sham-exposed rats. Percentages of male animals surviving to the end of the study did not vary by exposure group, although among females a decrease in survival time was seen in the cage control group who were not exposed to RF. The results for this study are similar to those seen in several other long-term Fischer 344 rat investigations designed to determine whether RF exposure promotes tumours initiated by administration of ENU prenatally.[10,11]

Smith and colleagues (2007)[12] exposed 65 male and 65 female Wistar rats to 902 MHz GSM or 1747 MHz Digital-Coded Squelch (DCS) signal at three nominal SAR values: 0.44, or 1.33, or 4.0 W/kg. Exposure was carried out for two hours per day, five days per week for 52 consecutive weeks (30 rats per group) or for 104 weeks (100 rats per group). During exposure the rats were confined in polycarbonate tubes within an electromagnetically isolated carousel. A sham-exposed and a cage control group were included in the study. At the end of the studies (52 weeks and 104 weeks exposure), rats which had survived were euthanized, and tissue from all rats was examined microscopically. No significant differences were seen between the RF-exposed and sham-exposed rats in body weight, mean individual organ weights, or numbers or types of non-neoplastic or neoplastic tumours.

Tillman and colleagues (2007)[13] designed a study to evaluate possible carcinogenic effects from RF field exposure in B6C3F1 mice. The mice were divided into groups of 65 and were exposed to 902 MHz GSM or 1747 MHz DCS signal at low (0.4 W/kg), medium (1.3 W/kg) or high (4.0 W/kg) SAR levels. Similar numbers of mice were assigned to either sham or to cage control status. Mice were exposed to RF fields or sham two hours per day, five days per week over a period of two years while restrained in tubes. Tubes were mounted in “ferris wheel” type exposure systems to equalize SAR to each rat within exposure categories. At the end of two years, surviving mice were euthanized. A uniform microscopic tissue examination was carried out on these mice and all mice dying in the course of the study. No differences in mortality during the course of the study or in tumour type or incidence rates were seen between RF-exposed and sham-exposed groups of mice.

A further study by Bartsch et al. (2010),[14] originally designed to study the effects of 902 MHz GSM long-term exposure on Sprague-Dawley rats, was unevaluable for cancer outcomes due to insufficient data and potentially inadequate pathologic examination of the animals.

All of the long-term bioassays evaluating spontaneous tumour development due to exposure to long courses of RF field exposure have been convincingly negative and were mostly carried out on 2G GSM-pulsed wireless systems.

Table 1. Cancer bioassays and RF field exposure in rat and mouse animal models

Study	Animal Species/ Strain	Exposure	Tumour	Results	Comments
Chou et al. (1992)[7]	200 Sprague-Dawley rats	2450 MHz pulsed signal; SAR 0.15–0.4 W/kg or sham for 21.5 hrs/day, 7 days/wk, for 25 mos	Spontaneous tumours	No significant difference in RF- exposed vs. control rats	Complete histopathology on all animals
LaRegina et al. (2003)[8]	480 Fischer 344 rats	835 MHZ FDMA or 847 MHz CDMA signal; SAR brain 0.85 W/kg or sham 4 hrs/day, 5 days/wk for 2 yrs	Spontaneous cancers	No significant difference in RF- exposed vs. control rats	Complete histopathology
Anderson et al. (2004)[9]	700 Fischer 344 rats	1600 MHz signal; SAR 0.16 or 1.6 W/kg or sham; 2 hrs/day, 7 days/wk for 2 yrs	Spontaneous cancers	No significant difference in RF- exposed vs. control rats	Complete histopathology
Smith et al. (2007)[12]	1170 Wistar rats	902 MHz GSM pulsed and handover; or 1747 MHz; SAR 0.4, 1.3 or 4.0 W/kg or sham 2hrs/day, 5 days/wk, for 1 or 2 yrs	Spontaneous tumours	No difference between 902 MHz or 1747 MHz RF-exposed vs. control rats	
Tillman et al. (2007)[13]	1170 B6C3F1 mice	902 MHz GSM and 1747 MHz DCS in basic and talk modes SAR levels of 0.4, 1.3, 4.0 W/kg; 2 hrs/day, 5 days/wk for 2 yrs	Liver tumours or their precursors	No effect of RF on hepato-cellular tumours	No health effects attributable to RF exposure

6B.4.2 Cancer in tumour- prone animals and RF exposure (Table 2)

Another group of cancer studies involves animals bred for susceptibility to a specific tumour. The study which galvanized interest in whether RF exposure might enhance cancer incidence in tumour-prone animals was conducted originally in 1997.[15] The investigators exposed Eμ-*pim*-1 transgenic mice (which develop lymphoma at a high rate) to 900 MHz GSM pulsed RF fields or sham twice per day for 30 minutes, seven days per week beginning at six to eight weeks of age and continuing up to 18 months at SAR values of between 0.13 and 1.4 W/kg. Mice were examined frequently during the course of the study for development of lymphoma. At the end of the study, those mice which had survived were discarded rather than being histopathologically examined—a weak point in the investigation as examination of all participating animals was therefore incomplete. A 2.4-fold increase in lymphoma was reported in the mice exposed to 900 MHz RF fields by comparison with sham animals.

Utteridge and colleagues (2002)[16] attempted to replicate the findings of the 1997 study. They exposed Eμ-*pim*-1 mice to a 898 MHz pulse modulated RF signal at SAR levels of 0.25, 1.0, 2.0, and 4.0 W/Kg one hour per day, five days per week for up to 104 weeks. Sham and cage control groups were also included in the study. Mice were restrained in plastic tubes during RF exposure, which took place on a carousel device designed to ensure uniform RF exposure to all mice in each group. Complete pathologic examination was carried out on all mice either at death during the study or at study termination. No significant differences in lymphoma incidence were seen between RF-exposed mice at any SAR level and sham-exposed animals.

A further attempt to replicate the findings of the 1997 study was conducted by Oberto et al.[17] using the same animal model (Eμ-*pim*-1). The investigators used restraints on the animals to achieve uniform exposure levels, from the pulsed 900 MHz, signal. The mice were exposed to whole body SAR values of either 0.5, 1.4, or 4.0 W/kg, or to sham exposure for one hour per day, 7 days per week for the duration of the study, with complete histologic examination of all mice. Compared to the sham-exposed controls, the RF-exposed animals had lower survival, which was statistically significant in the male mice but not in the female, and without an exposure-response gradient. However, no differences in lymphoma incidence were seen between the RF- and sham-exposed mice. The authors concluded that the results did not support a role of RF exposure in carcinogenesis.

A further study was completed by Sommer et al. (2007)[18] in a different mouse strain (AKR/J mouse) which develops leukemia/lymphoma as a result of incorporation of a virus into its genome rather than a transfected oncogene (cancer causing gene) as in the Eμ-*pim*-1 mouse. One hundred sixty (160) AKR/J mice in each study arm were either exposed or sham-exposed to a UMTS test signal (around 1950 MHz modulated at 1.6 GHz and designed to simulate UMTS power control in mobile phone calls) 24 hours per day for 248 days. Animals were unrestrained but were housed in an

elaborate metal mesh and perspex grid system which ensured even RF exposure. Results showed no differences in leukemia-lymphoma incidence or survival time between exposed and sham-exposed mice. Results seen in this study were the same as those seen in an earlier investigation by the same group in 2004[19] using a 900 MHz pulsed GSM signal instead of 1966 MHz UMTS.

Saran and colleagues (2007)[20] exposed newborn *Patched1* heterozygous knockout mice and their wild-type siblings to a uniform plane-wave 900 MHz GSM signal at a SAR of 0.4 W/kg or sham for 30 minutes twice per day for five days to determine whether RF fields increased risk of medulloblastoma, a type of brain tumour. The *Patched1* animal was chosen for this study because it is susceptible to development of medulloblastoma. No differences in tumour incidence or overall survival were seen between the exposed and sham-exposed groups at the end of the study. The authors concluded there was no evidence of a carcinogenic effect on the central nervous system (CNS) due to neonatal exposure to 900 MHz fields in this susceptible animal model after the 48-week duration study. It would appear that no other long-term assays have used this animal model, so no replication has been attempted.

Lee et al. (2011)[21] exposed AKR/J mice to the effects of both CDMA and WCDMA RF fields simultaneously. Six-week-old mice were exposed to 848 MHz CDMA and WCDMA carrier signal at 1950 MHz in a reverberation chamber for 45 minutes per day, five days per week for up to 42 weeks. SAR values for each exposure were 2.0 W/kg, 4 W/kg in total. A group of animals were sham exposed in the same chambers as part of the protocol. Comparison of lymphoma rates among groups at the end of the study revealed no significant difference between rates in the dual RF-exposed mice compared to the sham-exposed animals. The authors concluded that the results did not indicate a relationship between RF fields and lymphoma.

A series of studies were carried out prior to 2005 to evaluate whether C3H MMTV+ mice exposed to RF fields had a higher incidence of mammary tumours (data not tabulated).[22-25] This mouse carries the mouse mammary tumour virus and is highly susceptible to mouse breast tumours. After groups of mice were exposed by different researchers to RF fields for 16,[25] 18,[22,23] and 21[24] months duration, none showed any increased risk of mammary tumours by comparison with sham-exposed mice.

Table 2. Cancer and RF field exposure in tumour-prone animal models

Study	Animal Species/ Strain	Exposure	Tumour	Results	Comments
Utteridge et al. (2002)[16]	Eμ-pim-1 female mice	898 MHz GSM-pulsed signal; SAR 0.25–4.0 W/kg, 1 hr per day, 5 days/wk, up to 104 wks	Lymphoma	No significant difference in lymphoma incidence between RF-exposed mice at any SAR level and sham-exposed mice	Did not replicate Repacholi et al. (1997)[15] results
Oberto et al. (2007)[17]	Eμ-*pim*-1 mice	900 MHz pulsed at 217 HZ, 0.6 ms; SAR 0.5, 1.4, 4.0 W/kg or sham, 1 hr/day, 7 days/wk for 18 mos	Lymphoma	No difference between RF- and sham-exposed mice in lymphoma incidence	Mortality higher in RF-exposed groups than in control groups at SAR 0.5 W/kg but not at higher levels
Sommer et al. (2007)[18]	AKR/J female mice	UMTS 1.966 MHz; power control jumps; SAR 0.4 W/kg, or sham, 24 hr/day, 7 days/wk for 35 wks	Lymphoma	No difference in lymphoma incidence between RF- and sham-exposed mice	RF exposure had no effect on overall animal survival
Saran et al. (2007)[20]	Patched 1 hetero-zygous knock-out and wild-type mice	900 MHz; GSM; SAR 0.4 W/kg or sham for 0.5 hr 2x/day post natal day 2 thru 6	CNS tumours	RF-EMF had no effect on incidence of cerebellar tumours, basal cell carcinoma-like phenotype of rhabdomyo-sarcoma	No evidence that RF-EMF exposure affected survival in either $Ptc^{\pm}$ or wild-type mice
Lee et al. (2011)[21]	AKR/J mice	Combined CDMA (849 MHz) and WCDMA (1950 MHz); SAR 4.0 W/kg total for 45 min/day, 5 days/wk for 42 wks	Lymphoma	No increase in lymphoma in mice exposed to combined CDMA and WCDMA vs. sham-exposed mice	RF exposure had no effect on overall survival

6B.4.3 Cancer initiation/promotion and RF exposure

Another group of studies has been carried out using rats and mice to examine the possibility that RF might promote the development of cancer in animals previously exposed to a known carcinogen. These studies examine the effect of mobile phone RF field exposure in comparison to sham exposure on the incidence of tumours of the brain or central nervous system (CNS) chemically induced by N-ethylnitrosourea (ENU) and mammary tumours induced by 7, DMBA.

6B.4.4 CNS tumours (Table 3)

Shirai and colleagues (2005)[26] conducted a study to assess whether RF fields would increase the incidence of CNS tumours in Fischer 344 rats exposed in utero to 4 mg/kg of N-ethyl-N-nitrosourea (ENU), a potent mutagen and carcinogen, by comparison to mice exposed to the same chemical agent but not to RF fields. Rats were exposed to a 1439 MHz TDMA near field signal at SAR of 0.67 or 2 W/kg for 90 minutes per day, five days per week for 104 weeks or sham. A cage control group exposed neither to ENU nor to RF fields was also included. At the end of the study, surviving animals were euthanized and all animals, including those dying during the course of the study were histopathologically examined with the pathologist blind to the exposure status of animals. Results showed no increase in CNS tumour incidence in either the low or high RF+ENU rats by comparison to the rats with ENU and sham exposure. In addition, no effects were seen on levels of a number of important hormones, including ACTH, corticosterone or melatonin in RF+ ENU-exposed animals compared to those with sham exposure plus ENU.

Zook and Simmens (2006)[27] examined the possibility that RF exposure to Sprague-Dawley rats might increase risk of CNS tumours induced by 6.25 or 10 mg/kg ENU administered in utero. Rats were exposed to pulsed 860 MHz RF fields or sham in restraints in a “ferris wheel” exposure set-up, beginning on day 53 after parturition, for six hours per day, five days per week for between 171 and 325 days. At the end of 24 months, all surviving rats were killed and examined. No increase in incidence, multiplicity or latency of any type of CNS tumour was seen by addition of RF field exposure to either rats exposed to 6.25 mg/kg or 10 mg/kg of ENU by comparison to rats exposed to identical doses of ENU with sham RF exposure.

In 2007 Japanese investigators[28] evaluated the effect of exposure to 1950 MHz W-CDMA RF near field exposure (equivalent to that with use of a hand-held mobile phone on an IMT-2000 system) for two years on CNS tumour development after exposure to 4 mg/kg of ENU in utero. The study was similar to an earlier negative investigation conducted by the same research group using a Japanese mobile phone 1439 MHz TDMA signal.[26] A total of 500 Fischer 344 rat pups were divided into several groups treated with ENU alone, ENU plus RF at SAR levels of 0.67 or with 2 W/kg to the brain, or ENU and sham RF exposure. A fifth group comprising cage controls was also included in the protocol. Exposure to RF fields began at five weeks, 90 minutes per

day, five days per week for 104 weeks. Rats were restrained in tubes during exposure in order to ensure accurate RF exposure to the brain. At the end of the study, no significant increases in tumour incidence were seen in either males or females in the RF-EMF-exposed groups of rats by comparison with rats exposed in utero to ENU + sham exposure. In addition, no significant differences were seen in ACTH levels or levels of melatonin in RF-EMF-exposed animals compared to non-exposed. Two earlier 24-month studies by Adey and colleagues[10,29] using Fischer 344 rats exposed to in utero ENU and to 836 MHz fields also showed no increase in incidence of CNS tumours.

6B.4.5 Mammary and liver tumours (Table 3)

Several investigations have been conducted to examine the possible promotional effect of mobile phone RF signals on the incidence of rat mammary tumours (the rat analogue of breast cancers in women) induced by 7, 12-dimethybenz(a)anthracene (DMBA), a potent carcinogen and mutagen.

The study by Yu and colleagues (2006)[30] involved dividing 500 Sprague-Dawley rats into four groups which were initially treated with 35 mg/kg of DMBA. Three groups were then exposed to 900 MHz GSM signal with whole body SAR levels of 0.44, 1.33, or 4.0 W/Kg in an exposure wheel and a fourth comprising a control group with sham exposure. A cage control group treated with neither DMBA nor RF exposure was also included. RF field exposure commenced at day 48, the day after DMBA administration, and continued for four hours per day, 5 days per week for 26 weeks. At study completion, all animals were euthanized and necropsied. All pathologic examination (and RF exposure) was conducted with investigators blind to the exposure status of the animals. There were no significant differences in mammary tumour incidence between the sham-exposed controls and any of the GSM-exposed rat groups, nor any differences in time to tumour onset, or multiplicity, or size of tumours.

Mammary cancer incidence was examined in 500 DMBA-treated Sprague-Dawley rats divided into five groups, with three being administered increasing levels of exposure to pulsed 902 MHz fields giving SAR values of 0.44, 1.33, or 4.0 W/Kg for four hours per day, five days per week, for six months.[31] A fourth group was sham-exposed, and a cage control group was incorporated into the protocol. During exposure, the rats were restrained in polycarbonate tubes placed in a “ferris wheel” exposure set-up to ensure uniformity of RF fields throughout the study. During the course of the study, all animals were examined weekly to detect mammary tumours. At the end of the study, all remaining animals were sacrificed and pathologic examination of animals was conducted.

At the conclusion of the study, the rats with the highest SAR levels (4.0 W/Kg) from exposure to 900 MHz fields had developed a greater number of malignant mammary tumours than rats with lower SARs, but lower numbers of benign tumours. No dose-response gradient from lowest to highest SAR was seen, and in addition, the cage control animals without exposure to RF-EMF developed essentially the same number of

malignant mammary tumours as the rats in the highest exposure group, and even more benign tumours. The inconsistency of the results and lack of a dose-response gradient led the authors to conclude that the differences seen between the groups of animals were incidental and not attributable to RF-EMF exposure. Earlier studies by Bartsch et al. (2002)[32] and by Anane and colleagues (2003)[33] using Sprague-Dawley rats with mammary tumours induced by DMBA also demonstrated no role for 900 MHz pulsed GSM exposure in increasing incidence of the tumours.

No recent studies have evaluated liver tumours, but in an older Japanese study (1998),[34] unrestrained Fischer 344 rats were exposed to pulsed 929 MHz near field signal (SAR of between 1.9 and 0.9 W/kg at the liver) or sham for 90 minutes per day, five days per week for six weeks. The rats had previously been given a single dose of diethylnitrosamine (DEN) at six weeks of age. In addition, three weeks after commencement of RF exposure, all rats had a 2/3 partial hepatectomy. Six weeks after RF exposure began, animals were euthanized and examined for pre-neoplastic lesions in the liver by comparing the numbers and areas of the induced glutathione S-transferase placental form (GST-P)-positive foci in the livers of exposed and sham-exposed rats. No significant differences were seen between the RF- and sham-exposed groups. A further study by the same group[35] with Fischer rats but using 1439 MH TDMA signal instead of 929 MHz signal with the same exposure schedule as noted above, again found no indications that the RF fields promoted the induction of pre-neoplastic lesions in the liver.

6B.4.6 Skin tumours (Table 3)

Several recent bioassays evaluating the promotional effects of RF-EMF on skin cancers have been carried out fairly recently in mice.

A study by Huang and colleagues (2005)[36] using ICR mice examined whether RF exposure promoted skin tumours initiated by DMBA. Mice were shaved and given a single topical application of DMBA (100 µg/100 µl acetone per mouse). They were then randomized into four groups with exposure to a CDMA signal at 848.5 MHz, or 1762.5 MHz, or sham. A fourth group was exposed to 12-O-tetradecanoylphorbol-13-acetate (TPA) as a positive control group. The addition of positive controls, that is, a group in which it is certain that skin tumours will develop, can assist investigators in knowing what type of tumour to assess from DMBA and RF exposure. The maximum whole body SAR was 2.4 W/kg at 849 MHz and 12.2 W/Kg at 1763 MHz, but the average whole body exposure during the course of the study was 0.4 W/Kg. The RF schedule was two cycles of 45 minutes RF exposure, 15 minutes apart, five days a week, for 19 weeks. Although the TPA positive control group developed skin cancers as expected, no indication was found at the termination of the study after 20 weeks that either of the DMBA + RF-exposure mice or the sham-exposed group developed skin tumours or showed any perturbations in skin cell proliferation. The results indicate that DMBA and RF fields did not act together as co-carcinogens in genesis of skin cancer.

One other recent study by Paulraj and Behari (2001)[37] evaluated RF exposure in conjunction with DMBA in the generation of skin tumours (papillomas) in Swiss albino mice. Mice were divided into seven groups, one control, one with DMBA (100 µg) application only, groups with DMBA plus either 112 MHz RF amplitude modulated at 16 Hz (SAR of 0.75 W/kg) or 2450 MHz radiation (SAR of 0.10 W/kg), one with 112 MHz RF exposure only, and one with 2450 MHz exposure only. A seventh group acted as a positive control with application of DMBA plus croton oil. RF exposure for two hours per day, three days per week, was continued for 16 weeks. At study termination, skin tumours were seen only in the positive control group. No effect was seen with exposure to either 112 MHz or 2450 MHz fields alone or in combination with DMBA.

Table 3. Cancer initiators/promoters and RF field exposure in animal models

Study	Animal Species/ Strain	Exposure	Initiator/ Co-carcinogen	Tumour	Result	Comments
	CNS Tumours					
Shirai et al. (2005)[26]	Fischer 344 Rats	1439 MHz TDMA; SAR 0.67 or 2.0 W/kg to brain, or sham; 90 min/day, 5 days/wk for 104 wks	ENU in utero 4 mg/kg	CNS tumours	No signifi-cant increase in CNS tumours in RF-exposed vs. sham- exposed rats	No effect of RF exposure on ACTH, corticos-terone or melatonin levels
Zook and Simmens (2006)[27]	Sprague-Dawley rats	Pulsed 860 MHz signal; brain SAR 1.0 ± 0.2 W/kg or sham; 6hrs/day, 5 days/wk for 171–325 days	ENU at 6.25 or 10.0 mg/kg	CNS tumours	No effect on CNS tumour incidence malig-nancy, volume multipli-city latency	
Shirai et al. (2007)[28]	Fischer 344 Rats	1950 MHz W-CDMA signal; SAR 0.67 or 2.0 W/kg to brain or sham; 90 min/day, 5 days/wk for 104 wks	ENU in utero 4 mg/kg	CNS tumours	No effect of RF on incidence of CNS tumours	No effect of RF on ACTH, corticosterone or melatonin levels
	Mammary Tumours					
Yu et al. (2006)[30]	Sprague-Dawley female rats	900 MHz; SAR levels of 0, 0.44, 1.33, 4.0 W/kg, or sham; 4 hrs/day, 5 days/wk for 26 wks	Single dose of DMBA 35 mg/kg	Mammary tumours	No statistically significant elevation or reduction in mammary tumours in any RF- exposure group	
Hruby et al. (2008)[31]	Sprague-Dawley rats	902 MHz pulsed signal; SAR 0.4, 1.3, or 4.0 W/kg or sham; 4 hrs/day, 5 days/wk for 6 mos	Single dose of DMBA	Mammary tumours	More malignant tumours in highest SAR RF group than mid or low but about same as the cage controls. No dose-response gradient by RF dose	Authors noted that differences between RF groups are incidental rather than attributable to RF exposure

Study	Animal Species/ Strain	Exposure	Initiator/ Co-carcinogen	Tumour	Result	Comments
	Liver Tumours					
Imaida et al. (2001)[35]	Fischer 344 rats	1439 MHz near field TDMA; SAR liver 0.9–1.37 W/kg, 90 min/day, 5 days/wk for 6 wks	DEN 200 mg/kg + partial hepatectomy	Pre-neoplastic liver lesions	1439 MHz RF does not promote liver cancer	
	Skin Tumours					
Huang et al. (2005)[36]	ICR mice	849 MHz or 1763 MHz CDMA real signal or sham (whole body SAR 0.4 W/kg); 90 min/ day, 5 days/wk for 19 wks	10 µg dose of DMBA at 7 wks for all mice	Skin tumours	No joint effect of exposure to 849 or 1763 MHz + DMBA on incidence of skin cancers	
Paulraj and Behari (2011)[37]	Swiss albino mice	112 MHz AM signal at 16 Hz or pulsed 2450 MHz or sham; 2 hrs/day for 14 wks	Single dose 100 µg DMBA; DMBA and croton oil as positive control	Skin tumours	No effect of 112 MHz or 2450 MHz RF alone or with DMBA on skin tumour genesis	

Summary

Long-term bioassays have long been considered the "gold standard" for investigations of carcinogenicity in animals. Studies conducted using RF field exposure alone as a tumour-initiator have been convincingly negative even with exposures of two years. Further, these studies have exposed rats and mice to RF levels over the course of the animals' lives, which substantially exceed levels seen in humans. The animal evidence therefore would indicate that it is very unlikely that RF exposure alone would be carcinogenic to humans.

The investigations of RF radiation as a tumour promoter in conjunction with known carcinogens have also been negative, and again, at levels above those seen in day-to-day human exposure.

The studies cited in this review are of very high quality. Most feature full microscopic assessment of multiple tissue samples in experimental animals, with the pathologist "blind" to the exposure status of the animals. They also include accurate RF dosimetry, with animals either restrained during exposure to ensure precise SAR levels in specific tissues or exposed in reverberation chambers to allow movement while preserving accurate whole body SARs. The lack of any body of evidence showing a strong association between any tumour and RF exposure, the lack of dose-response relationships, and the lack of analogous findings with human cancer in the epidemiologic data, all important criteria for causal associations[38] militate against any suggestion that RF field exposure alone initiates or promotes the growth of cancer in animals. Repacholi et al. (2012)[39] in a recent comprehensive review including bioassay results for cancers of the central nervous system, found no compelling evidence of RF radiation carcinogenicity in animal studies.

6B.5 Toxicologic Studies and RF Exposure

6B.5.1 DNA damage and RF exposure (Table 4)

An early study by Lai and Singh (1996)[40] exposed Sprague-Dawley rats to 2450 MHz pulsed or continuous wave RF fields or sham for two hours at 1.2 W/kg whole-body SAR. On examination of brain tissue immediately after exposure, an increase in both single- and double-strand DNA breaks were seen in the animals exposed to pulsed or continuous wave RF compared to sham-exposed rats. A similar experiment, conducted by the same investigators in 2004[41] exposed rats to either a 2450 MHz field alone, a temporarily incoherent magnetic field alone, both exposures together or sham and again found higher levels of single and double strand DNA breaks in rats exposed solely to 2450 MHz fields than sham-exposed rats; however, those exposed to both the RF fields and the temporarily incoherent magnetic field appeared to have no more DNA breaks than sham-exposed animals.

An attempt was made by a European group, specifically Verschaeve et al. (2006),[42] to replicate the results of Lai and Singh (1996)[40] using Wistar rats exposed to pulsed 900 MHz GSM signal for two hours per day for a period on 24 months (SAR 0.4 W/kg), for two hours per day, five days per week for 24 months. In addition, the animals were also exposed to the potent mutagen/carcinogen 3-chloro-4-(-dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) in their drinking water throughout the study. Other rats were exposed to MX alone. Double-strand DNA breaks were analysed using the alkaline Comet assay. The Comet assay assesses DNA damage by applying pulsed gel electrophoresis to DNA extracted from test animals. This results in a "comet like" figure as negatively charged DNA fragments migrate toward the positive pole. The amount of DNA in the "comet tail" is used as the measure of DNA damage. In rats exposed to MX, damage was seen, as expected, in blood liver and brain cell DNA, but in the rats exposed to the 900 MHz radiation as well as MX, no increase was seen in DNA damage over MX alone. The authors concluded that the results provided no indication that RF fields enhanced MX DNA damage.

Belyaev and colleagues (2006)[43] also attempted to replicate the results of the 1996 study[40] by Lai and Singh. Fischer 344 rats were exposed to 915 MHz GSM signal at a whole body SAR of 0.4 W/kg or sham in a transverse electromagnetic transmission (TEM) cell for two hours. Use of the TEM cell enabled accurate whole body exposure while allowing animals to move around. At the conclusion of the study, examination of brain cells found no evidence of increased DNA double-strand breaks by comparison with sham exposed rats.

Micronucleus formation and chromosomal aberrations are indications of DNA damage, and several studies have evaluated micronucleus formation in tissues of animals exposed to RF fields. Ferreira and colleagues[44] exposed pregnant Wistar rats to 834 MHz RF signal for 8.5 hours from gestation to birth at SAR values of 0.55–1.23 W/kg or

sham. At birth, the animals were sacrificed and an increased level of micronucleus formation was seen in the bone marrow of RF-exposed versus sham-exposed animals.

The joint Belgian-Finnish study noted above[42] also assessed micronucleus formation but found no increased formation in rat brain and liver samples of the RF-exposed animals by comparison with those exposed to MX alone. Gurbuz et al. (2010)[45] exposed Wistar rats to an 1800 MHz modulated GSM signal applied 20 minutes per day, five days per week for one month and found no increase in micronucleus formation in exfoliated bladder cells from rats exposed to the RF fields by comparison with control rats.

Table 4. Toxicologic changes and RF field exposure in animal models

Study	Animal Species/ Strain	Exposure	Results	Comments
Lai and Singh (1996)[40]	Sprague-Dawley rats	2450 MHz pulsed or CW signal; SAR 1.2 W/kg or sham for 2 hrs	Increased single- and double-strand breaks in RF- exposed rat brain	
Lai and Singh (2004)[41]	Sprague-Dawley rats	2450 MHz CW signal; SAR 0.6 W/kg; or 45 mG magnetic field, or both, or sham for 2 hrs	Increased single- and double-strand DNA breaks in RF-exposed rat brain	Increase in DNA breaks in RF-exposed rats attenuated by concurrent magnetic field
Verschaeve et al. (2006)[42]	Wistar rats	900 MHz pulsed signal; SAR 0.3 or 0.9 W/kg + 19 µg/ml MX mutagen in water or MX and sham RF exposure; 2 hrs/day, 5 days/wk for 24 mos	No increased DNA damage in brain and liver tissue of rats exposed to RF and MX compared to MX alone; no increase in micronuclei	
Belyaev et al. (2006)[43]	Fischer 344 rats	915 MHz GSM signal pulsed SAR 0.4 mW/g or sham for 2 hrs	No increased DNA damage in RF-exposed rat brain cells than sham-exposed	
Ferriera et al. (2006)[44]	Wistar rat pups	834 MHz; SAR 0.55–1.23 W/kg; 8.5 hrs/day from gestation to birth or sham	Increased erythrocyte micronucleus formation in RF-exposed pups	
Gurbuz et al. (2010)[45]	Wistar rats	1800 MHz GSM pulsed signal for 20 min/ day, 5 days/wk, for 1 mo or sham	No increased micronuclei in exfoliated bladder cells in RF vs. control animals	

6B.5.2 Reactive oxygen species and RF exposure

Production of reactive oxygen species occurs in normal physiological processes involving oxygen. While small levels of reactive oxygen species have a role in physiologic processes such as apoptosis, they also contain free radicals which, at high concentrations, can damage DNA.

Two studies[46,47] exposed female Wistar rats to pulsed 900 MHz or sham exposure for 30 days and showed increased levels of malondialdehyde in the endometrium of exposed rats. Malondialdehyde is a molecular indicator of lipid peroxidation which generates reactive oxygen species. Of interest, the authors noted that increasing levels of vitamin C or E in the diet appeared to ameliorate potentially damaging reactive oxygen species. Most studies of reactive oxygen species with RF exposure are conducted using cellular model systems rather than animals, and these investigations are outlined in Section 6A (Cellular Studies).

6B.5.3 Apoptosis and RF exposure (Table 5)

Apoptosis, or programmed cell destruction, is a process whereby a cell initiates a process of self-destruction when significant toxic or genetic damage accumulates. While the normal process of apoptosis ensures that an animal (or human) retains healthy cells, the appearance of significant numbers of apoptotic cells in experimental animals may indicate dangerous conditions for cell survival. Dasdag and colleagues[48] exposed Wistar rats to either 900 MHz GSM signal at SAR levels from 0.17–0.58 W/kg or sham two hours per day, 7 days per week for 10 months to look for signs of apoptosis in brain cells or indications of increase in reactive oxygen species. Cage control animals were included in the study as well as the sham rats. Apoptosis scores in the RF-exposed animals proved to be lower than those in the sham-exposed or cage control rats. In addition, no significant differences were seen between the three groups in oxidative stress index levels.

A rabbit animal model was also used to evaluate apoptosis levels after exposure to RF fields.[49] Two strains (California and New Zealand rabbits) were exposed to 650 MHz broadcast signal or sham 24 hours per day for a period of two years. After two years exposure, some RF-exposed animals were sacrificed immediately and some were retained for another 1.5 years post-exposure prior to killing. Results of examination of brain tissue showed an increased number of apoptotic cells in the animals exposed to RF fields and sacrificed after 24 months exposure, and a further increase in such cells in rabbits left for a further 1.5 years before sacrifice, compared to sham and cage control animals.

Investigators in Korea exposed C57BL mice to RF fields at 849 MHz and 1763 MHz (as used in a Korean mobile phone system) or sham for one hour per day, five days per week for periods of up to one year.[50] Exposure was conducted with animals restrained in order to ensure good control of exposure to the brain. At six months and at one year, groups of exposed and sham mice were humanely killed and brain tissue examined. No indications of increased apoptotic cells were seen in RF-exposed vs. sham-exposed animals.

French[51] and Japanese scientists[52] conducted studies of RF exposure in Fischer 344 rats exposed to 900 MHz and 915 MHz GSM fields respectively. Both studies were designed to evaluate blood-brain permeability and are described in detail in the following

section; however the results of both studies showed no increases in indicators of apoptosis in the brain cells of RF-exposed rats compared with sham-exposed animals.

Table 5. Apoptosis and RF field exposure in animal models

Study	Animal Species/ Strain	Exposure	Result	Comments
Dasdag et al. (2009)[48]	Wistar rats	900 MHz GSM signal; SAR 0.17–0.58 W/kg or sham; 2 hr /day, 7 days/wk for 10 mos	Decrease in apoptosis in RF-exposed rats.	
Tarantino et al. (2005)[49]	California and New Zealand rabbits	650 MHz broadcast signal; SAR 3.4 W/kg or sham; 24 hrs/day for 52 wks	Increase in apoptotic cells in brain tissue of RF-exposed vs. sham-exposed animals	Dosimetry description is confusing
Kim et al. (2008)[50]	C57BL mice	849 MHz or 1763 MHz signal; SAR 7.8 W/kg; or sham; 1 hr/day, 5 days/wk for 6 or 12 mos	No indications of increased cell apoptosis in RF-exposed animals compared to sham	
Poulletier de Gannes et al. (2010)[51]	Fischer 344 rats	915 MHz GSM signal; SAR 0.14 or 2.0 W/kg for 2 hrs or sham	No apoptotic neurons detected	
Masuda et al. (2009)[52]	Fischer 344 rats	915 MHz GSM signal; SAR levels of 0.02, 0.2, or 2.0 W/kg or sham for 2 hrs	No increase in apoptotic cells in RF-exposed vs. sham-exposed rats	Followed closely the protocol of Salford et al., 2003

6B.5.4 Gene expression and RF exposure (Table 6)

Studies of gene expression in animals are designed to determine whether exposure to RF fields alters the way in which genes code for production of polypeptide chains and ultimately proteins in living animal systems. Genes and their expression ultimately control processes such as cell differentiation and proliferation and cell death, organ structure, and other functions in animals and humans. Although gene expression changes may not all be considered genotoxic, they are grouped here with other toxicologic studies for convenience.

Belyaev and colleagues (2006)[43] used an Affymetrix U34A gene chip to probe some 8800 genes to evaluate expression changes in the brains of eight Fischer 344 rats exposed for two hours to pulsed 915 MHz signal at a whole body SAR of 0.4 W/kg. Gene chips such as the Affymetrix device used in this study hold DNA probes from one of DNA's double helices, and these can recognize the corresponding DNA from the other helix in experimental samples. The chips allow analysis of a large number of potential gene variants quickly and at relatively low cost. On analysis, the study found 11 up-regulated genes and one down-regulated. The genes were reported as encoding for a variety of functions including neurotransmitter regulation as well as blood-brain barrier permeability and melatonin production. The authors noted that because of the small number of rats used in the study and the limited power, the results should be treated cautiously.

Finnie (2005)[53] exposed C57BL/6NTac mice to pulsed 900 MHz GSM signals or sham for a period of 60 minutes. After the exposure, brains of the animals, in addition to those of a cage control group of mice, showed no greater c-*fos* (a marker of neuron activity) expression among mice subjected to acute exposure to short-term RF fields compared to sham-exposed mice. The exposed and sham mice were restrained during exposure, however, and analysis showed higher levels of *c-fos* expression in the restrained animals (RF- and sham-exposed) than in cage controls, suggesting that stress levels in animals may be a potential confounder in gene or protein expression studies.

The same group[54] followed their earlier study with an assessment of longer-term exposure to pulsed 900 MHz fields using similar methods to those in the 2005 investigation described above. C57BL/6Ntac mice were exposed 60 minutes per day, five days per week, for 104 weeks and showed no effect of RF field exposure on *c-fos* expression in the brain by comparison with the sham exposed mice.

Paparini and colleagues (2008)[55] evaluated gene expression in the brain tissue of Balb/cJ mice using the Affymetrix Mouse Expression Array 430A (a chip which includes more than 14,000 mouse gene probes) after a single one-hour exposure to 1800 MHz GSM radiation (average brain SAR 0.2–0.56 W/kg) or sham exposure in a transverse electromagnetic (TEM) cell (a device which ensures a consistent and uniform RF frequency field). The investigators conducted a preliminary analysis using as a cut-off point a greater than 1.5-fold increase or decrease in expression by comparison with that expected, and showed that 301 probes were differentially expressed in the RF-exposed mice. However, they determined that a more stringent analysis was necessary because the many comparisons made between normal and test values would produce a significant number of false-positive findings due to chance alone. After the more stringent analysis, the authors concluded that no significant differences in gene expression were found between the RF-exposed and sham-exposed animals.

A further evaluation by Finnie and colleagues (2009)[56] was conducted to see whether exposure to RF fields in utero might induce a stress response in the brains of fetal mice as indicated by induction of heat shock proteins Hsp32 or Hsp70. Pregnant Balb/c mice were exposed to a 900 MHz GSM field 60 minutes per day for the entire gestational period of 19–20 days at a SAR level of 4.0 W/kg. At gestation, the pups were killed and their brains were analysed, but no differences were seen in Hsp32 and Hsp70 in the RF- versus sham-exposed mice.

Taken together, the literature has produced some indications that RF exposure might cause gene expression changes in animals exposed to such fields, but most studies did not. Replication of the positive studies has been lacking, and even where changes in expression level appeared to occur, these changes have not yet been shown to result in change in gene function. With increasing use of high-throughput techniques for gene expression studies in future, there is a potentially high false discovery rate[57,58] as some genes will be over- or under-expressed by chance alone. However, researchers

working in this area are aware of this issue and appear to be adjusting their statistical testing procedures to minimize false positives.

Table 6. Gene expression and RF field exposure in animal models

Study	Animals Species/Strain	Exposure	Result	Comments
Finnie et al. (2005)[53]	C57BL/6NTac mice	900 MHz pulsed signal; SAR 4 W/kg (whole body) or sham for 1 hr	*c-fos* expression in brain same in RF- and sham-exposed mice	Cage control arm had lower expression of *c-fos* in brain compared to RF and sham arms
Belyaev et al. (2006)[43]	Fischer 344 rats	915 MHz GSM pulsed signal; SAR 0.4 W/kg or sham for 2 hrs	11 up-regulated and 1 down-regulated gene in brain tissue	
Finnie et al. (2007)[54]	C57BL/6NTac mice	900 MHz pulsed GSM signal; SAR 4 W/kg (whole body) or sham; 1 hr/day 5 days/wk, for 104 wks	*c-fos* expression in brain tissue same in RF- and sham-exposed mice	Cage control (unrestrained) animals had lower *c-fos* expression than RF and sham arms
Paparini et al. (2008)[55]	Balb/cJ mice	1800 MHz GSM signal SAR (brain) 0.2–0.56 W/kg or sham for 1 hr	No consistent evidence of gene expression modulation by RF field exposure in brain tissue	
Finnie et al. (2009)[56]	Balb/C mice	900 MHz pulsed GSM signal in utero SAR 4 W/kg or sham; 60 min/day for 19–20 days	No difference in induction of Hsp32 or Hsp70 in RF- compared to sham-exposed mice	

Summary

The recent studies of putative toxicological changes due to RF radiation in animals have been characterized by superior means of animal restraint to control RF exposure to specific organs, better control of thermal effects, and better descriptions of experimental protocols than studies published prior to 2004–2005. Characterization of RF dosimetry is still a weak point only in a few studies. However, these improvements have not contributed to more consistent evidence for an effect of RF exposures on physiological processes in animals. Results of studies of DNA damage, micronucleus formation, apoptosis, production of reactive oxygen species, gene expression changes, and other genotoxic effects carried out using RF exposure of animal models (mice and rats) tend to be contradictory. Positive results found in one species are usually not replicated. Overall, the criteria important in establishing a causal relationship between short-term or long-term RF exposure and changes in gene expression, apoptosis, production of reactive oxygen species and other potential biologic changes in animal physiology are lacking. Such criteria include consistency of results over several studies among similar animals and strong associations between exposure and response with control for potential confounding factors. This lack of consistent evidence reduces the likelihood that significant adverse physiologic effects occur in animal models due to RF exposure.

6B.6 Central Nervous System and RF Exposure

6B.6.1 Blood- brain barrier and RF exposure (Table 7)

A number of experimental studies have been conducted in animal models to determine whether exposure to RF fields alters the permeability of the blood-brain barrier. The presence of very tight junctions between endothelial cells in central nervous system capillaries serves to restrict access to the brain of bacteria and other substances to a much higher degree than in other organs of the body. Integrity of this barrier is one of the reasons that bacterial infections in the brain are rare. Reduction in tightness of this barrier, if caused by RF field exposure, could therefore have significant adverse health effects in humans.

Initial concern was raised by a study conducted by a group of scientists from Lund University in Sweden in 1994.[59] In 2003 the Swedish group[60] exposed Fischer 344 rats 12–26 weeks of age to 915 MHz continuous wave and pulsed GSM signal or sham exposure for a period of two hours in a TEM cell at three SAR levels (2, 20 or 200 mW/kg). After exposure, the rats were observed for 50 days and sacrificed. Examination revealed increased permeation of albumin from capillaries into both white and grey brain matter in RF-exposed rats by comparison with sham-exposed animals, suggesting that exposure to pulsed RF fields at around 900 MHz increases permeability of the blood-brain barrier. They also observed an increase in "dark neurons," indicators of neuronal damage in rat brains in animals exposed to RF fields.

The latest study by the Swedish group (2009)[61] investigated the effect of RF exposure on Fischer rats in a TEM cell. The rats were divided into groups and were exposed to a 900 MHz GSM signal from a mobile phone at SAR levels of 0.0012, 012, 0.12 W/kg or sham for a period of two hours. After a recovery period of seven days, the animals were sacrificed and necropsied. The investigators found significant foci of albumin leakage in grey and white matter surrounding capillaries in the rats exposed to 0.012 W/kg. More modest levels of extravasation were seen at other SAR levels.

Finnie and colleagues in Australia (2006)[62,63] initiated several studies to see if younger animals might be more sensitive to potential blood-brain barrier permeability with exposure to RF fields. Balb/c mice were exposed to 900 MHz GSM pulsed RF signal or sham 60 minutes per day either in utero (gestational days 1–19) or for seven days after birth. The protocols included cage control and a positive control group which had had a single injection (2 mg/kg) of cadmium chloride, a substance known to disrupt the blood-brain barrier. Although extravasation was seen in the brains of the positive control animals, no indications of increased albumin extravasation were seen in either in utero or early life RF-exposed mice by comparison with sham and cage control animals.

An investigation by Turkish scientists (2009)[64] also reported leakage. Their study utilized a Wistar rat model with exposure to 900 or 1800 MHz continuous wave near

field signal or sham for a period of 20 minutes at 12.6 V/m. No SAR value was given in the paper. Evans blue dye was employed as a tracer material injected into tails of the rats 20 minutes prior to RF exposure. Brains of the rats were examined immediately after RF exposure and leakage of Evans blue stain into the brain in male (but not female) rats was seen with exposure to 900 or 1800 MHz signal. It is not clear why significant differences in permeability were seen between exposed and sham male rats, but similar findings were not seen in female rats.

The Japanese study of Masuda et al. (2009)[52] exposed Fischer 344 rats to 915 MHz pulsed fields at SARs up to 2.0 W/kg or sham for a period of two hours in a TEM cell following as closely as possible the protocol described by Salford et al. (2003).[60] Separate cold and chemical injury rats were also included in the protocol as positive controls. At days 14 and 50, RF-exposed and sham rats were sacrificed and their brains evaluated. No elevated levels of extravasation or "dark neurons" were seen in RF-exposed rats compared to sham-exposed controls. The authors reported that the results failed to confirm the Swedish study.

An American study (2009)[65] exposed Fischer 344 rats to 30 minutes of 915 MHz continuous wave and 915 MHz pulsed wave RF fields at SARs from .0020–20 W/kg or sham in TEM cells. Animals were restrained during exposure in order to ensure good control of RF exposure to the brain, and positive brain injury controls as well as cage control rats were included in the protocol. After examination of the brains of all the animals, no increases in extravasation were found in any of the RF-exposed groups by comparison with sham-exposed or cage control rats.

Poulletier de Gannes and colleagues in France (2010)[51] conducted a very similar study to that of Salford et al. (2003)[60] using Fischer rats exposed to 915 MHz GSM for two hours at SARs of 0.14 W/kg, or 2 W/kg or sham. This study also optimized RF exposure to the brain using animal restraints, resulting in very precise RF exposure. The study included cage controls as well as cold injured positive controls. After 14 and 50 days the rats were killed and brains examined. Again no evidence of leakage across the blood-brain barrier was seen in RF-exposed rats by comparison with sham-exposed animals.

Finnie et al. (2009)[66] exposed mice to 900 MHz pulsed far field RF at SAR of 4 W/kg or sham for 60 minutes per day, 5 days per week for a much longer period of time than previous studies (104 weeks). Cage control and chemical brain-injured (clostridium toxin) positive control groups were also included. In addition, this study used a somewhat more sensitive outcome measure for extravasation than albumin release as an indicator of increase in permeability of the blood-brain barrier, namely up-regulation of the water channel protein AQP-4 in the brain. After examination of brain tissue at the end of the study, no detectable up-regulation of AQP-4 was seen in the RF-exposed mice, while the chemical-injured positive control animals, as expected, showed substantial up-regulation.

Sirav and Seyhan (2011)[67] completed a similar study to their earlier investigation,[64] again in Wistar albino rats, and once again found that exposure to 900 or 1800 MHz RF fields for 20 minutes promoted a significant increase in albumin in the brains of male rats by comparison with sham-exposed animals. However, inexplicably no significant increase was seen in the RF-exposed female rats.

Table 7. Blood-brain barrier permeability and RF field exposure in animal models

Study	Animal Species/ Strain	Exposure	Result	Comments
Salford et al. (2003)[60]	Fischer 344 rats	915 MHz CW and pulsed signal; SAR 2, 20, or 200 mW/kg or sham for 2 hrs	Albumin leaking into white and grey matter + "dark" or degenerating neurons in RF-exposed vs. control rats	Observations made 50 days post RF exposure
Finnie et al. (2006)[62]	Balb/c mice	900 MHz far field signal in utero; SAR 4 W/kg, or sham; 60 min/day, day 1–19 gestation	No albumin extravasation in RF-exposed or sham or cage control mice	
Finnie et al. (2006)[63]	Balb/c mice	900 MHz GSM pulsed far field signal; SAR 4 W/kg for 60 min/day for 7 days postnatally	No albumin extravasation in RF-exposed or sham or cage control mice	
Nittby et al. (2009)[61]	Fischer rats	900 MHz GSM signal from a mobile phone for 2 hours SAR of 0.0012, 0.012, or 0.12 W/kg or sham with 7 days recovery	Albumin positive foci around vessels in white and grey matter at 0.012 W/kg + dark neurons	Animals exposed in transverse electromagnetic transmission line (TEM) cell
Sirav and Seyhan (2009[64]	Wistar albino rats	900 MHz at 13.5 V/m or 1800 MHz at 12.6 V/m CW near field or sham exposure for 20 min	Increased extravasation of Evans blue dye in brain of male but not female exposed rats compared to sham	No SAR value given
Masuda et al. (2009)[52]	Fischer 344 rats	915 MHz pulsed at 16 or 217 Hz for 30 min, SAR of 0.02, 0.2 or 2.0 W/kg or sham- exposed in TEM cell	No increased extravasation of albumin in exposed rats	Cold- and chemical-control rats positive. Negative replication of Salford et al. (2003)[60]
McQuade et al. (2009)[65]	Fischer 344 rats	915 MHz CW and pulsed signal; SAR 0.002, 0.02, 0.2, 2.0 or 20 W/kg; or sham for 30 min	No significant increase in albumin extravasation in any RF- exposed vs. sham- or cage-control rats	RF exposure from protocol of Salford et al. (2003)[60]
Poulletier de Gannes et al. (2010)[51]	Fischer 344 rats	915 MHz GSM signal; SAR 0.14 or 2.0 W/kg for 2 hrs or sham	No increase in albumin extravasation in RF-exposed vs. sham- exposed and cage control rats. No dark neurons detected	Same basic protocol as Salford et al. (2003)[60]
Finnie et al. (2009[66]	Balb/c mice	900 MHz pulsed far field signal; SAR 4 W/kg or sham for 60 min/day, 5 days/wk, for 104 wks	No increase in AQP-4 expression in RF-exposed mice	
Sirav and Seyhan (2011)[67]	Wistar albino rats	900 MHz CW at 4.7 V/m, (SAR 4.26 mW/kg) or 1800 MHz CW (SAR 1.46 mW/kg) or sham for 20 min	Increased extravasation of Evans blue dye in brain of male- but not female-exposed rats compared to sham	

Summary

Recent studies have improved on the methods used in the mainly positive earlier studies[59,60] on blood-brain barrier permeability including improved procedures for tissue fixation, and albumin staining and more accurate and better described RF dosimetry.[68]

In addition, many of the recent studies[51,52,65,66] have incorporated positive control animals which are given brain injuries known to cause extravasation, and these studies have shown the expected extravasation in the injured animals but not in the RF-exposed ones. Overall, the weight of evidence for an adverse effect of RF-EMF on the integrity of the blood-brain barrier appears to have been considerably decreased based on results from most recent studies. A relatively recent review of the evidence on the effect of RF-EMF on blood-brain barrier permeability presented at a scientific meeting[69] concluded that such exposure had no adverse effect in the absence of significant tissue temperature increase.

6B.6.2 Brain physiology and behaviour and RF exposure (Table 8)

Concerns with the potential effects of RF exposure on physiologic processes within the brain have resulted in more than 30 studies since 2006. These include studies of changes in gene expression, apoptosis, and a variety of other potential effects.

Brillaud and colleagues (2007)[70] assessed the effects of acute exposure of 15 minutes to 900 MHz (SAR levels of 1.6 and 6.0 W/kg). The animals were killed at days 2, 3, and 10 post-exposure and brain tissue was examined. Results showed an increase in brain concentrations of glial fibrillary acidic protein (GFAP). GFAP is a protein expressed by astrocytic brain cells and is thought to be important in cell communication. However, the increase in GFAP levels was highest two days post-exposure, with a reduced level at three days, and none at 10 days, indicating that the GFAP increase was likely transitory.

A similar study by the same group, Ammari and colleagues, 2008,[71] examined the effect of pulsed 900 MHz GSM exposure on GFAP in Sprague-Dawley rats. The animals were exposed for 45 minutes per day at 1.5 W/kg or 15 minutes per day at 6 W/kg, five days per week, or sham exposed for 24 weeks. The rats were restrained during exposure for more precise RF dosimetry. Cage control animals were included in the study. Ten days after exposure was completed, the animals were sacrificed and brain tissue examined. At a SAR level of 6 W/kg, the exposure was associated with significant increases in levels of GFAP. It should be noted that this SAR level is much higher than seen with normal human RF exposure.

A further study by Ammari et al. (2010)[72] using a similar protocol to the study using Wistar rats, applied pulsed 900 MHz RF signal 45 minutes per day for eight weeks. Analysis of tissue from the several parts of the brain, namely the prefrontal cortex, cerebellar cortex and dendate gyrus at three and 10 days post-exposure indicated

elevated levels of GFAP, suggesting that the RF exposure was having a physiological effect, at least on astrocytic cells in the central nervous system.

Yilmaz et al. (2008)[73] found no brain changes after exposing Sprague-Dawley rats to 900 MHz GSM signal in speech mode for 20 minutes per day for one month. Similarly, Dasdag et al. (2009)[48] reported no significant changes in p53 activity in glial cells of Wistar rats after exposure to 900 MHz RF for two hours per day, seven days per week for 10 months, by comparison with that in sham-exposed rats.

Bas et al. (2009)[74] exposed Wistar rats to continuously modulated 900 MHz GSM signal (SAR 2.0 W/kg) or sham for one hour per day for 28 days and found a significant decrease in pyramidal cells in the brain of the exposed rats by comparison with sham- exposed animals. Pyramidal cells are thought to play an important role in cognitive functioning.

A study by Maskey et al. (2010)[75] showed loss of pyramidal cells in the hippocampus, a part of the brain involved in cognitive function, in mice after exposure to 835 MHz CDMA signal for a period of eight hours per day for three months at SAR levels of 1.6 W/kg.

Finnie et al. (2010)[76] examined acute and a long-term RF exposure to determine whether physiologic indicators of stress in the brains of mice could be evinced by exposure to pulsed 900 MHz GSM fields using a different measure of activity: microglial activation. Microglial cells are resident immune cells which are normally quiescent but in the presence of injury, toxic challenge or other stressors, are activated and become mobile. Mice were given a either a single whole-body exposure at SAR of 4.0 W/kg for 60 minutes or a series of such exposures on five successive days per week for 104 weeks. Other groups of mice were sham exposed. No increase in microglial activation detectable was seen in the short-term single 60-minute RF-exposed mice versus sham-exposed mice, or in the long-term two-year RF-exposed mice versus the sham-exposed comparison groups.

Table 8. Physiological changes in the brain and RF fields

Study	Animal Species / Strain	Exposure	Results	Comments
Brillaud et al. (2007)[70]	Sprague-Dawley rats	900 MHz pulsed signal; SAR 6 W/kg; single 15 min exposure	Increased GFAP in RF-exposed rats compared to sham at 3 days, none at 10 days	
Ammari et al. (2008)[71]	Sprague-Dawley rats	900 MHz pulsed GSM signal; SAR 1.5 W/kg 15 min/day or SAR 6 W/kg or sham; 15 min/day 5 days/wk for 24 wks	Increased GFAP stained area in brains of rats exposed to 6 W/kg but not 1.5 W/kg	
Ammari et al. (2010)[72]	Sprague-Dawley rats	900 MHz pulsed GSM signal; SAR 1.5 W/kg or 6 W/kg or sham; 45 min/day, 5 days/wk, for 8 wks	Increased GFAP in rats exposed to RF at both SAR levels vs. sham	

Study	Animal Species/ Strain	Exposure	Results	Comments
Bas et al. (2009)[74]	Wistar albino rats	900 MHz modulated signal; SAR 2 W/kg (head) or sham; 1 hr/day for 28 days	Decrease number of pyramidal cells in cornu-ammonis area of brain in RF vs. sham rats	
Maskey et al. (2010)[75]	ICR mice	835 CDMA signal; SAR 1.6 W/kg 8 hrs/day for 3 mos or sham	Loss of pyramidal cells in RF-exposed animals compared to sham	
Dasdag et al. (2009)[48]	Wistar albino rats	900 MHz; SAR 0.17–0.58 W/kg (head) or sham; for 2 hrs/day, 7 days/wk for 10 mos	p53 not changed by RF exposure compared to sham-exposed rats	
Finnie et al. (2010)[76]	Mice; strain not named	900 MHz pulsed signal; SAR 4 W/kg; or sham for 60 min; or for 60 min 5 days/ wk for 104 wks	No increase in microglial activation in acute or long-term RF- exposed mice compared to sham mice	Positive control group showed substantial microglial activation

Summary

The results of a number of studies indicate that exposure to RF frequencies commonly used in mobile phone technology may produce some changes in the brains of both rats and mice. There are some concerns with the methodology of the positive studies; for instance, reported changes in GFAP levels at SAR levels of 6 W/kg raises the possibility that focal thermal changes rather than the RF exposure itself might have affected the outcome measure. These levels are much higher than humans are exposed to in day-to-day use of electronic devices. Moreover, some of the changes may be of short duration with reversion after cessation, at least for the effects of acute exposure. The relevance of these effects in animals and in humans is an open question, and more research will be needed to try to confirm the positive results and clarify their importance. In particular, long-term studies might be useful as most of the animal investigations carried out have been relatively short term.

6B.6.3 Behavioural studies and RF exposure (Table 9)

Several studies have been conducted using animal models to determine whether exposure to RF fields at low power levels can alter behaviour, disrupt learning, or affect cognitive function.

Lai (2004)[41] subjected three groups of rats to either an incoherent magnetic field alone, a 2450 MHz RF continuous field at a SAR of 1.2 W/kg, incoherent magnetic field (30–100 Hz field at 6 μT) + RF exposure, or sham exposure for one hour prior to each of six training sessions designed to teach the rats to locate a submerged escape platform in a water maze. One hour after the last training session, the platform was removed and the rats were subjected to a further test to assess the time spent swimming in the area the platform was previously located versus other areas of the water maze. Results showed that the group of rats exposed to RF only had a significant deficit in time spent in the previous platform location by comparison with sham-exposed animals. However,

the superimposition of the incoherent magnetic field on RF exposure appeared to attenuate somewhat the deficit seen in the rats exposed to 2450 MHz fields alone. No effect was seen in rats exposed to the incoherent field alone. The author concluded that exposure to the RF field may have induced temporary spatial learning and memory deficits but that the deficits could be attenuated by superimposition of the incoherent magnetic fields.

The findings from this investigation launched a series of studies to try to replicate an effect of RF fields on spatial learning. The initial studies by Cobb et al. (2004)[77] and Cosquer and colleagues (2005)[78] in rats using a water maze and 2450 MHz pulsed exposure with the same study protocols (although without the incoherent magnetic field exposure) found no difference between performance in the RF-exposed rats compared to the sham-exposed.

In a further study conducted by Kumlin et al. in 2007,[79] a group of 24 juvenile rats was exposed to a pulsed 900 MHz GSM signal for two hours each day, five days per week or sham beginning 24 days post-natal and continuing until age eight weeks. At the end of exposure, 18 of the RF- and sham-exposed rats were subjected to performance tests in a Morris water maze. The exposed rats showed significantly lower escape times than sham-exposed animals. The remaining six animals were sacrificed, and necropsy showed no effect on brain morphology, or blood-brain barrier permeability compared to the non-exposed rats.

Ammari et al. (2008)[80] subjected groups of rats to a pulsed 900 MHz GSM signal for 15 minutes per day at a high specific absorption rate (SAR 6.0 W/kg) or 45 minutes per day at a lower rate (SAR 1.5 W/kg) or sham for eight weeks or 24 weeks, and found no consistent differences between RF-exposed rats and sham-exposed rats in spatial memory. Cage control animals were found to have poorer performance in the test than either experimental group, but the authors attributed this to lack of daily handling, indicating that factors such as this need to be carefully controlled in future studies.

A further study by Narayanan et al. (2009)[81] was conducted by placing a mobile phone in vibratory mode at 900/1800 MHz GSM beneath the floor of a cage containing juvenile rats. Each day for four weeks the unrestrained rats were exposed to the fields associated with 50 missed calls with the phone in "vibrate" mode. At assessment of their spatial learning capabilities, the RF-exposed rats were found to take a longer time than control rats to locate an escape platform. However, the RF-exposure results may have also been confounded by the effects of the vibration of the phone on the rats. The study has also been criticized because the exposure protocol made it impossible to make realistic estimates of the actual RF exposure to the rats.

A Florida-based research group[82] conducted a study in which A□PPsw transgenic mice (which suffer from Alzheimer's-like cognitive symptoms) and their non-transgenic littermates were evaluated in a water maze, with initial results showing that the transgenic mice were, as expected, impaired compared to their non-transgenic

littermates. Beginning at five months of age, the mice were exposed to a 918 MHz GSM field at a SAR of 0.25 W/kg for two periods of one hour each day or sham exposure. After 6–7 months exposure to RF fields, transgenic mice showed significantly improved performance on most of the test measures compared to the sham-exposed transgenics. Some improvement was also seen in the RF-exposed non-transgenic mice compared to the sham-exposed littermates. However, the RF-exposed animals had a rectal temperature 1˚C higher than the non-exposed animals, which is high for the reported SAR of 0.25 W/kg, so it is possible that other factors in the exposure protocol may have affected the findings.

Table 9. Behavioural change and RF field exposure in animal models

Study	Animal Species/ Strain	Exposure	Results	Comments
Lai (2004)[41]	Sprague-Dawley rats	2450 MHz CW signal; SAR 1.2 W/kg with or without 30–100 Hz magnetic field, 6 μT for 1 hr	Rats exposed to RF field had increased water maze escape time by comparison with sham	Increased escape time may indicate memory or learning deficits
Cobb et al. (2004)[77]	Sprague-Dawley rats	2450 MHz pulsed signal; SAR 0.6 W/kg or sham; 45 min/day for 10 days	No significant differences in water maze escape time or errors between RF-exposed and sham rats	
Cosquer et al. (2005)[78]	Sprague-Dawley rats	2450 MHz pulsed signal; 0.6 or 2 W/kg; 45 min/day for 10 days	No difference in water maze errors made by RF-exposed rats compared to sham-exposed	
Kumlin et al. (2007)[79]	Wistar rats	900 MHz GSM signal; SAR 3 W/kg; or sham; 2 hrs/day, 5 days/wk for 5 wks	Improved performance in water maze among RF-exposed rats compared to sham-exposed	Examination of brain tissue showed no morphology changes in RF-exposed rats
Ammari et al. (2008)[80]	Sprague-Dawley rats	900 MHz GSM signal; SAR 6 W/kg (brain) for 15 min or 1.5 W/kg for 45 min; 5 days/ wk for 8 or 24 wks	No consistent differences in spatial memory task between RF- exposed rats and non-exposed	
Narayan et al. (2009)[81]	Wistar rats	900–1800 MHz GSM phone signal; 50 missed calls per day for 4 wks or no exposure control	Spatial learning capacity of rats in RF-exposed groups compromised by comparison with control animals	No SAR given; phone on "vibrate" setting may have altered RF-rats response
Arendash et al. (2010)[82]	AβPPsw (transgenic) mice	918 MHz GSM signal; SAR 0.25 (whole body) 1 W/kg (brain); 1 hr/day from age 2 mos for 7 mos, or from age 5 mos for 8 mos	After 5–6 mos RF exposure transgenic rats showed improved water maze performance over their initial performance. No change in sham-exposed mice	RF exposure raised body temperature > 1˚C.

Summary

Like many of the other facets of RF exposure on animals, research on effects on behaviour and cognition are mixed, with several studies showing that RF exposure has an adverse effect, but most showing no effect or even improved performance. The

studies were, in general, fairly well conducted, using appropriate methods. Unfortunately, no variable such as RF frequency, duration of exposure, or period of life of the animal has emerged as being consistently associated with behavioural effects. However, much of the research in this field is still exploratory in nature, and it is difficult to judge the body of evidence to date. More studies are needed in this field of research.

6B.7 Somatic Systems and RF Exposure

6B.7.1 Immune function and RF exposure (Table 10)

Several studies of immune function in the presence of RF fields have been conducted since 2005.

Nasta et al. (2006)[83] examined the effect of RF exposure on a number of immunologic parameters in C57BL/6 mice including frequency of several types of B and T cells important in immune function and production of antibodies in the spleen. Groups of mice separated within polycarbonate containers were exposed to 900 MHz GSM signal in a TEM cell at a SAR of 2 W/kg. RF exposure or sham continued for two hours per day, five days per week for four consecutive weeks. A jacket containing circulating water was positioned under the floor of the exposure set-up to keep temperatures stable during RF exposure and ensure against thermal effects. Results showed that the frequency of differentiating transitional 1 and 2B (T1, T2) cells, or mature follicular B and marginal zone B cells in the spleen were unaffected by exposure to RF fields in comparison with sham-exposed mice. An in vitro antibody production test was conducted on spleen cells from non-immunized RF field-exposed and sham-exposed mice. Antibody production by spleen cells was unaffected by RF exposure. The authors concluded that the study offered no support for the theory that RF exposure may alter B-cell peripheral compartment and antibody production.

Prisco and colleagues (2008)[84] examined the ability of cells from C57BL/6 mice exposed to RF fields by comparison with those from sham-exposed animals to repopulate marrow in mice exposed to marrow-lethal X-irradiation. The mice were exposed in a TEM cell to 900 MHz GSM modulated signal or sham for two hours per day, five days per week for four weeks. After exposure, bone marrow cells from the RF-exposed and sham mice were injected into X-irradiated mice. At three weeks and six weeks post-exposure, transplanted mice were killed and immune components were examined. Results showed no differences between cell populations in the marrow of mice transplanted with marrow from RF-exposed and sham-exposed mice, or in production of interferon γ, a cytokine produced by natural killer and natural killer T-cells critical in immune modulation.

Perhaps the most important recent studies in immune function relating to RF field exposure are two investigations conducted in France and Russia to replicate early reports in Soviet journals[85,86] suggesting adverse effects on the immune systems of rats

resulting from chronic 2375 MHz RF exposure at electric field levels of 5 W/m^2. Although SAR levels were not presented in the original series of papers, this power density would be associated with values of about 0.6 W/kg. The Soviet studies indicated RF exposure disrupted the antigenic structure in rat brain cells. The exposure also produced modification in the number of plasmocytes in the spleen and the number of small lymphocytes in the marrow, perhaps due to an autoimmune reaction in the animals. Further, the studies showed that intraperitoneal injection of serum from chronically RF-exposed animals into non-exposed pregnant rats resulted in increased fetal mortality and decreased weight in their offspring compared to that seen in pregnant rats receiving non-RF-exposed rat serum injection. French[87] and Russian[88] scientists launched independent studies (but with a common protocol) to try to confirm or refute the Soviet results.

The Russian study (2010)[88] exposed Wistar rats to 2450 MHz continuous wave RF far field (whole body SAR 0.16 W/kg) or sham in an anechoic chamber for seven hours per day, five days per week for a period of 30 days. At seven days post-exposure, some of the animals were sacrificed and examination using complement fixation tests showed minor increases in antibody production in the brain (but not in liver) tissue extract in the RF-exposed rats compared to sham rats. In addition, at seven and 14 days post-exposure, serum taken from exposed and sham rats was injected intraperitoneally into pregnant rats. Among the pregnant rats injected with serum from the RF-exposed rats, embryo mortality at day 20 of pregnancy was higher by comparison with that seen in the dams injected with serum from the sham-exposed rats. Postnatal offspring mortality comparing pregnant cage control rats with sham and RF-injected pregnant rats was planned in the study but was hampered by unaccountably high mortality (34%) among rats in the cage control group. No comparisons of offspring mortality among RF, sham and cage control rats were therefore presented in the paper, presumably because the unknown factors leading to the high mortality among cage control animals might conceivably have affected the RF- and sham-exposed rat groups.

The French study (2009)[87] followed the same protocol as the Russian study.[88] The French group did not repeat the complement fixation tests of the Russian group for antibodies in brain tissue because the differences between the RF- and sham-exposed groups were regarded as not important. They used ELISA tests (which use optical density to quantitatively assess antibody prevalence) exclusively to test for production of antibodies to brain and liver tissue. Sixteen antigens were used to test against IgA, IgM and IgG immune globulins and analysis of the ELISA data showed no significant differences in antibody production in brain and liver tissue samples between cage control, sham or RF-exposed rats. Among the pregnant rats injected intraperitoneally with serum taken at days 7 and 14 post-exposure from RF-exposed, sham-exposed and cage control rats, no significant differences were seen in the number of live and dead fetuses during pregnancy, or number of pups, sex ratio, mean body weight, viability or physical development to age 28 days. The authors concluded that the results did not support the original Soviet findings.

Due to the differences in the results of the two studies, the WHO EMF Project convened an international oversight committee[89] to review the results of the two studies. They determined that the more subjective aspects of interpreting the complement fixation tests to determine antibody levels in the Russian study rendered those results questionable, particularly when an error analysis carried out by the international oversight committee determined that the differences seen between the RF- and sham-exposed tests would have been expected due to normal variation when employing this methodology. The significant differences in intrauterine fetal mortality between rat dams injected with RF- and sham-exposed serum in the Russian study was felt to be questionable due to the extraordinarily high mortality among the cage control (and the RF- and sham-exposed) pups postnatally, suggesting that factors other than those under study were likely to have influenced study prenatal results.

Table 10. Immune function and RF field exposure in animal models

Study	Animal Species/ Strain	Exposure	Result	Comments
Nasta et al. (2006)[83]	C57BL/6 mice	900 MHz GSM modulated signal; SAR 2 W/kg or sham for 2 hrs/day, 5 days/wk for 4 wks	No changes in B-cell peripheral differentiation or antibody production from RF exposure	
Prisco et al. (2008)[84]	C57BL/6 mice	900 MHz GSM modulated signal; SAR \2 W/kg, 2 hrs/day, 5 days/wk, for 4 wks	No effect from RF exposure on spleen B or T cell percentages proliferation rates or γ IFN production in transplanted mice	RF-exposed cells transplanted into mice which have undergone marrow-lethal x-rays
Poulletier de Gannes et al. (2009)[87]	Wistar rats	2450 MHz CW signal; SAR 0.16 W/kg or sham for 7 hrs/day, 5 days/wk for 30 days	No differences in antibody levels in RF- exposed vs. sham-exposed rats; no differences in embryo mortality in dams injected with RF- exposed vs. sham-exposed serum	
Grigoriev et al. (2010)[88]	Wistar rats	2450 MHz CW signal; SAR 0.16 W/kg (whole body) or sham; 7 hrs/day, 5 days/wk, for 30 days	Higher antibody levels in RF-exposed mice brain but not liver; embryo mortality higher in dams injected with RF-exposed serum than sham serum	Unaccountably high mortality in cage control dams prevented comparison of offspring immune characteristics

Summary

The major concern from early Soviet studies that RF-EMF fields could affect the immune system of animals, and that the increased risk for adverse effects could be transmitted to offspring through serum injection, has not been confirmed by the well-conducted French study. The WHO international oversight committee which examined the results of both the Poulletier de Gannes et al. (2009)[87] and Grigoriev et al. (2010)[88] studies concluded that the weight of evidence from both studies taken together indicated that

intraperitoneal injection of serum from rats exposed to RF exposure is unlikely to influence development and mortality among fetuses of pregnant rats and unlikely to affect pup mortality postnatally. The number of animals used in each study (48 each) was relatively small and even though the results of the two studies indicated the absence of effects due to RF exposure, they lacked the power to be definitive. The Russian authors continue to maintain that their results support at least some of the earlier Soviet observations.[90] The committee recommended against repeating the studies, as this was not apt to increase knowledge in this field. Instead they recommended that investigators should, in future, pursue possible immune effects of RF fields in children if they prove more susceptible to RF-related adverse immune effects. Unfortunately, the same caveats noted earlier to reaching definitive conclusions about other adverse health effects of RF fields also apply to immune effects—namely that the RF frequency, duration of exposure, possible biologic mechanism, and outcome measures of primary importance remain unknown.

6B.7.2 Endocrine function and RF exposure (Table 11)

Most of the focus in animal studies of endocrine function has been on investigations of the influence of RF exposure on melatonin synthesis. Bakos and others (2003)[91] exposed adult male Wistar rats to a 900 MHz-modulated GSM signal at SAR values of 0.009–0.012 W/kg or sham, or 1800 MHz-modulated GSM signal at SARs of 0.02–0.45 W/kg or sham. The exposure was conducted in a TEM cell with animals exposed for two hours between 8:00 am and 10:00 am on even days and 10:00 am to noon on odd days daily for 14 days. Urine was collected from the animals from 12:00 am to 8:00 am and analysed for melatonin secretion. No significant differences were seen in rats with either 900 MHz or 1800 MHz RF field exposure compared with sham-exposed rats.

Koyu and colleagues (2005)[92] also conducted a study to determine the effects of RF exposure on melatonin secretion. Sprague-Dawley rats were exposed to either 900 MHz GSM or 1800 MHz signal at SAR levels of 2 W/kg or sham for 30 minutes per day, five days per week for four weeks. Melatonin was measured in serum using radioimmune assay, and no significant differences in levels were seen in rats exposed to either 900 or 1800 MHz fields by comparison with sham-exposed rats.

Hata et al. (2005)[93] examined the effect of a 1439 MHz TDMA signal at 2 W/kg whole body (7.5 W/kg head) on melatonin production in Sprague-Dawley rats. Animals were exposed for four hours on day 1 during a “dark” period in the lab to either 1439 MHz RF or sham. Cage control and light control animals were also included in the protocol. Blood and pineal glands were removed and melatonin and serotonin concentrations assessed. Results showed no differences in melatonin or serotonin levels in the RF-exposed rats compared to sham-exposed rats.

Lerchl and colleagues (2008)[94] exposed hamsters for 24 hours per day for 60 days to RF fields at 383 MHz, 900 MHz and 1800 MHz at whole body SARs of 0.08 W/kg or sham. Melatonin concentrations in sera and from pineal gland homogenates collected

from the animals at the end of the study showed no significant differences between RF-exposed animals at any of the three wavelengths and the sham-exposed controls.

Table 11. Endocrine function and RF field exposure in animal models

Study	Animal Species/ Strain	Exposure	Result	Comments
Bakos et al. (2003)[91]	Wistar rats	900 MHz signal; SAR 0.009–0.012 W/kg or 1800 MHz GSM signal; SAR 0.02–0.045 W/kg or sham; 2 hrs/day (at 08:00 or at 10:00) for 14 days	No significant effect on melatonin secretion in RF-exposed vs. sham-exposed rats	
Koyu et al. (2005)[92]	Sprague-Dawley rats	900 or 1800 MHz CW signal SAR 2 W/kg (max) or sham; 30 min/day, 5 days/wk for 4 wks	No significant effect on melatonin secretion from RF exposure	Time of exposure not given in the study
Hata et al. (2005)[93]	Sprague-Dawley rats	1439 MHz TDMA signal SAR 2 W/kg (7.5 W/kg head) for 4 hrs	No significant effect from RF exposure on melatonin	
Lerchl et al. (2008)[94]	Djugarian hamster	900 or 1800 MHz GSM or 383 MHz signal; SAR 0.08 W/kg, 24 hrs/day for 60 days	No effect of RF exposure on melatonin	

Summary

Studies of melatonin levels in animals have been negative, and the data provide no support for the possibility that RF exposure can decrease melatonin levels.

6B.7.3 Testicular function

Because of concern among the general public that exposure to RF electromagnetic fields might affect reproductive capacity, a number of studies on semen analysis have been conducted. These are summarized along with mechanistic studies and human investigations in Section 10 of the report.

6B.7.4 Female reproductive function and RF exposure (Table 12)

In Korea, Lee and colleagues (2009)[95] evaluated the effect of exposure to 3G code division multiple access (CDMA) and wideband code division multiple access (WCDMA) RF signals at SAR levels of 2 W/kg in ICR mice. Groups of pregnant dams (and their fetuses) were exposed to either 848.5 MHz CDMA or 1950 MHz WCDMA signal or both simultaneously for two sessions of 45 minutes each for days 1–17 of gestation. On day 18, all dams were humanely killed and examined for numbers of viable fetuses, number of dead fetuses, fetal weights, and a number of other measures. In addition, fetuses were examined for gross physical malformations, weight, body length, and skeletal malformations. No differences were seen in any of the outcome measures between the RF-exposed dams and sham-exposed dams. No differences in malformations, weight, length or other characteristics were seen in RF-exposed fetuses compared to sham-exposed fetuses.

Similar negative results were seen in a study of pregnancy outcome and visceral and skeletal abnormalities among offspring in pregnant Sprague-Dawley rats exposed to 1900 MHz WCDMA for 90 minutes per day on days 7–17 of gestation[96] and in pregnant C57BL mice (and fetuses) exposed to 1766 MHz UMTS signal or sham 24 hours per day in a series of studies involving four mouse generations.[97]

Investigators in Japan[98] exposed pregnant Sprague-Dawley rats to 2140 MHz WCDMA downlink signals in a search for adverse pregnancy outcomes, including visceral and skeletal abnormalities in offspring. Pregnant rats were exposed at two different relatively low SAR levels (0.028–0.040 W/kg or 0.066–0.093 W/kg) for 20 hours per day from gestational day 7 to postnatal day 21. No abnormalities were seen in the RF-exposed first generation (F1) offspring. After weaning, F1 offspring were removed from the exposure boxes, and at 10 weeks of age randomly selected males and females were isolated for breeding. After mating, pregnant dams were sacrificed at gestational day 20 and all F2 fetuses removed and examined for abnormalities. No abnormalities in fertility and embryo loss were seen in the RF-exposed F1 dams, and no visceral or skeletal abnormalities were found in their F2 offspring attributable to RF exposure.

Sambucci et al. (2010)[99] examined pregnancy outcome and immunologic function in C57 BL/6 mice after exposure while restrained to a 2450 MHz pulsed Wi-Fi signal at a SAR level of 4 W/kg or sham two hours per day from gestational day 5 through 19. No significant effects were seen on spleen cell number, B-cell frequency or antibody serum levels in the RF-exposed dams compared with sham-exposed animals. In the offspring, assessed at five and at 26 weeks of age, no immunologic effects were seen in in utero RF- exposed offspring compared to those not exposed.

Fragopoulou and colleagues (2010)[100] in Greece completed a study using BALB/c mice exposed in utero to 900 MHz GSM RF fields at SAR levels of 0.60–0.94 W/kg for six or 30 minutes per day from gestational days 0–21 and found an initial delay in ossification of cranial bones in RF-exposed pups compared to sham-exposed animals. However, this difference disappeared by day 35 after birth. An actual phone may have been used to provide RF exposure, casting some doubt on the RF dosimetry.

A number of other investigations not shown in Table 12[101-103] likewise found no effects of RF exposure.

Table 12. Female reproductive function and RF field exposure in animal models (2009–2011)

Study	Animal Species/ Strain	Exposure	Results	Comments
Lee et al. (2009)[95]	Pregnant ICR mice and their offspring	848.5 MHz CDMA (SAR 2.0 W/kg) and/or 1950 MHz WCDMA signal; SAR 2.0 W/kg in utero or sham for 2 sessions of 45 min each for days 1–17 of gestation	No adverse effects seen in offspring exposed to CDMA, WCDMA or both signals	Lack of thermal effects confirmed by rectal temperature before and after RF
Ogawa et al. (2009)[96]	Pregnant Sprague-Dawley rats	1900 MHz WCDMA signal SAR 0.67 or 2 W/kg to mother or sham; 90 min/ day on days 7–17 gestation	No effects seen in mothers or offspring	
Sommer et al. (2009)[97]	C57BL mice	1966 MHz UMTS 24 hrs/day lifelong; SAR 0.08, 0.4, 1.3 W/kg, or sham; as each set of pups is weaned, parental animals sacrificed; experiment continues over 4 generations	No effects on fertility, number and development of pups attributable to RF	
Takahashi (2010)[98]	Sprague-Dawley rats	2140 MHz downlink WCDMA signal 20 hrs/day from gestational day 7 through postnatal day 21; SAR dams 0.028–0.040 W/kg, or 0.066–0.093 W/kg); SAR fetuses 0.061–0.067 W/kg or 0.143–0.156 W/kg or sham	No adverse results in F1 dams or their offspring due to exposure to RF	
Sambucci et al. (2010)[99]	C57BL/6 mice	2450 MHz pulsed signal; SAR 4 W/kg or sham; 2 hrs/ day from gestation days 5–19	No significant effects on immunologic functions in mouse offspring	Animals restrained for accurate dosimetry to fetuses
Fragopoulou et al. (2010)[100]	Pregnant BALB/c mice	900 MHz signal from mobile phone in talk mode; SAR 0.6–0.94 W/kg, or sham; 6 or 30 min/day from gestational days 0–21	Initial delay in ossification in cranial bones of offspring; no effects by day 35	Actual mobile phone may have been used for exposure

Summary

Studies in female animals examining the putative adverse effects of RF fields on litter size, aspects of the health of offspring, prevalence of congenital abnormalities at birth and other endpoints have been almost uniformly negative, and there seems little probability, in animals at least, of adverse effects from in utero exposure to RF fields.

6B.7.5 Longevity and RF exposure

Although none of the two-year cancer bioassays have found differences in longevity between RF-exposed and non-exposed animals, two interesting studies in rats have recently been completed (data not tabulated). Adang et al. (2009)[104] in Belgium exposed four-month-old Wistar albino rats to 970 MHz pulsed or continuous wave or sham RF exposure two hours per day, seven days per week during a 21-month period.

After 14 and 18 months exposure, the white blood cell count in the continuous wave exposed rats was elevated by comparison with the sham-exposed group. After 24 months, mortality in the animals in both the pulsed and continuous wave-exposed groups appeared to be somewhat higher than that in the sham-exposed group although the results were not statistically significant.

Bartsch and colleagues (2010)[14] conducted a series of four experiments with female Sprague-Dawley rats. In the first two experiments, the rats were exposed to 900 MHz signal pulsed at 217 Hz or to sham exposure, starting at 52–70 days after birth and continuing until they were 580 or 770 days old; in neither experiment did any adverse effects materialize in the RF-exposed group by comparison with the sham-exposed group. In experiments 3 and 4, RF exposure was maintained even longer in the animals' lives. In experiment three, after 799 days, median survival was lower in the RF exposed group, and a similar finding was seen in the rats in experiment four after 852 days by comparison with the sham group. The authors noted that month of birth is known to influence lifespan in these animals and so results should be interpreted with caution; as well, seasonal influences in diet may contribute to discrepancies in lifespan among rats, although no information is presented in the paper on these factors.

Summary

The results of the two studies, while quite "soft," suggest that more attention needs to be paid to very long-term effects of RF-EMF. Although it is impossible to suggest a biologic mechanism which might explain the findings, results of both studies described above suggest that lifelong exposure to RF fields may shorten lifespan, perhaps in conjunction with other factors, at least in animals. As noted, several issues cloud the findings, and variables such as animal strain and environmental conditions under which animals are kept may be important, as well as diet. Studies commissioned as part of the US National Toxicology Program's cellular phone RF series, and currently underway, should be able to more closely monitor a variety of factors which affect animal lifespan while evaluating the independent effect of RF. Reports on these studies are to be available in 2014. A brief fact sheet is accessible at:

http://www.niehs.nih.gov/about/assets/docs/cell_phone_fact_sheet.pdf

6B.8 Discussion

Overall, studies in animals have not provided convincing evidence of major adverse effects from exposure to RF-EMF fields. Many new studies have been undertaken and completed since 2005, with improvements in study design and in execution by comparison with earlier efforts. Findings from most studies for a variety of biologic effects have been negative.

Investigations of the carcinogenicity of RF field exposure in animals have been virtually uniformly negative, and even studies of RF-EMF as a promoter in conjunction with known

carcinogens offer little evidence of adverse effect. Studies conducted with animals known to be at high risk of CNS, mammary, and other cancers have also been negative.

Studies of genotoxic effects, gene expression and apoptosis have yielded inconsistent results. One of the difficulties in going forward is that no specific frequency, timing or duration of exposure appears to distinguish positive studies from negative ones.

Investigations of putative effects of RF fields on the brain and central nervous system have found no consistent evidence of effect at the field strengths to which human beings are exposed to on a day-to-day basis. There was some indication of transitory increases in specific brain proteins and loss of pyramidal cells; however, further evaluation of these findings is needed in future studies. Most recent investigations of blood-brain barrier leakage have not found an increase in permeability due to exposure to RF-EMF. The newer studies have controlled more carefully for thermal effects which are known to alter blood-brain barrier permeability. They have incorporated improvements in methods for fixating brain specimens and techniques for visualizing changes in neural tissue. The addition of positive control groups as well as cage and sham controls have also provided useful comparison measures. Concern about increased blood-brain barrier permeability due to RF fields has been substantially reduced by results of recent investigations.

Behavioural studies aimed at evaluating adverse or beneficial effects of RF-EMF on spatial memory in animals have been mixed to date, with most studies showing no overall differences between RF- and sham-exposed animals; but other areas of brain function have yet to be thoroughly studied.

Recent reports on attempts to confirm early Soviet reports of adverse immune effects in rat embryos and in rat pups exposed in utero to 2450 MHz RF fields[87] were completely negative. The Russian[88] study did produce results indicating some support for the suggestion in early Soviet studies that injection of serum taken from animals exposed for 30 days to 2450 MHz fields and injected into pregnant rats might cause adverse effects in their embryos during gestation. However, problems with excess mortality in the RF- and sham-exposed animals and particularly in cage control rats cast doubt on any positive findings from the Russian study. After examination of the French and Russian protocols and results by an international oversight committee appointed by the World Health Organization,[90] the positive results seen in the Russian studies were effectively discounted. No other aspects of immune function in animals have been shown to be influenced by RF exposure in recent studies.

The results of studies of the effect of RF-EMF on pregnancy and reproductive function in female animals have been overwhelmingly negative.

To date, relatively little attention has been paid to the issue of whether young animals are more susceptible to adverse effects due to RF field exposure than older animals. A recent review of the relatively scant evidence generated from studies designed to address other issues has suggested that there is no strong support for vulnerability of

young animals to RF.[105] However, as immune function in many animals is immature at birth, the international oversight group, which reviewed studies presented by French and Russian scientists, specifically recommended further investigations in young animals exposed to RF fields by comparison to sham-exposed animals.

While the results of animal studies to date do not provide evidence for any strong or consistent biologic effects from exposure to RF fields, some caution is in order. Most positive results in animal studies have not been replicated in subsequent investigations, in part due to the wide variety of exposure methods, animal strains, and RF signal characteristics employed by investigators. Closer comparability of protocols, animal strains, and RF dosimetry employed in studies is not likely to take place in the immediate future as it is not known what frequency ranges, characteristics (pulsed or continuous wave) and duration and intensity of exposure are most important for effects to occur. Furthermore, no specific animal model or period of life has been identified as being most useful in studies of RF exposure. Perhaps the most important problem for future research in this area is the lack of a plausible mechanism by which RF exposure might cause adverse biological effects. Such a mechanism would surely sharpen the focus of future research.

A large series of studies on the effects of RF exposure in animal models is currently being sponsored by the National Toxicology Program within the National Institute for Environmental Health Services in the US. Reports on these studies, expected in 2014, may provide more definitive information.

6B.8.1 Research limitations and gaps in the literature

Several research limitations were apparent in the reviewed studies. There is a need for:

- Consistent use of a uniform set of criteria for describing RF exposure in animal studies and a possible model for such criteria
- Consistent use of good restraint methods designed to minimize animals' stress and thermal effects during exposure. Restraints will also improve the precision of field application where organ-specific exposure is required by a research protocol
- Consistent use of good containment vessels such as reverberation chambers for ensuring uniform RF fields for animals undergoing RF exposure in experiments where restraints are inappropriate.
- Research gaps include the need for:
    - Better more sensitive methods and more quantitative models for investigation of potential effects of RF exposure on animal behaviour
    - Studies of the very long-term effect of RF exposure with follow-up to the end of animals' natural life where this is economically feasible
    - Direct comparison studies of RF effects in young vs. adult animals of the same strain for a variety of potential biologic outcomes.

6B.9 References

1. Park HG, Han SI, Oh SY, Kang HS. Cellular responses to mild heat stress. Cell Mol Life Sci. 2005 Jan;62(1):10-23.
2. Ziemann C, Brockmeyer H, Reddy SB, Vijayalaxmi, Prihoda TJ, Kuster N, et al. Absence of genotoxic potential of 902 MHz (GSM) and 1747 MHz (DCS) wireless communication signals: In vivo two-year bioassay in B6C3F1 mice. Int J Radiat Biol. 2009 May;85(5):454-64.
3. Kuster N, Torres VB, Nikoloski N, Frauscher M, Kainz W. Methodology of detailed dosimetry and treatment of uncertainty and variations for in vivo studies. Bioelectromagnetics. 2006;27(5):378-91.
4. Latin American Experts Committee on High Frequency Electromagnetic Fields and Human Health. Non-ionizing electromagnetic radiation in the radiofrequency spectrum and its effects on human health. Campinas/SP, Brasil: Instituto Edumed - Edumed Institute for Education in Medicine and Health Independent Research Group on the Impacts of Mobile Technologies on Health; 2010 Jun. Available from: http://www.wireless-health.org.br/downloads/LatinAmericanScienceReviewReport.pdf.
5. Health Protection Agency. Health effects from radiofrequency electromagnetic fields. London, UK: HPA; 2012 Apr. Available from: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1317133826368.
6. Beyer LA, Beck BD, Lewandowski TA. Historical perspective on the use of animal bioassays to predict carcinogenicity: evolution in design and recognition of utility. Crit Rev Toxicol. 2011 Apr;41(4):321-38.
7. Chou CK, Guy AW, Kunz LL, Johnson RB, Crowley JJ, Krupp JH. Long-term, low-level microwave irradiation of rats. Bioelectromagnetics. 1992;13(6):469-96.
8. La Regina M, Moros EG, Pickard WF, Straube WL, Baty J, Roti Roti JL. The effect of chronic exposure to 835.62 MHz FDMA or 847.74 MHz CDMA radiofrequency radiation on the incidence of spontaneous tumors in rats. Radiat Res. 2003 Aug;160(2):143-51.
9. Anderson LE, Sheen DM, Wilson BW, Grumbein SL, Creim JA, Sasser LB. Two-year chronic bioassay study of rats exposed to a 1.6 GHz radiofrequency signal. Radiat Res. 2004 Aug;162(2):201-10.
10. Adey WR, Byus CV, Cain CD, Higgins RJ, Jones RA, Kean CJ, et al. Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats exposed to frequency-modulated microwave fields. Cancer Res. 2000 Apr 1;60(7):1857-63.
11. Zook BC, Simmens SJ. The effects of 860 MHz radiofrequency radiation on the induction or promotion of brain tumors and other neoplasms in rats. Radiat Res. 2001 Apr;155(4):572-83.

12. Smith P, Kuster N, Ebert S, Chevalier HJ. GSM and DCS wireless communication signals: combined chronic toxicity/carcinogenicity study in the Wistar rat. Radiat Res. 2007 Oct;168(4):480-92.
13. Tillmann T, Ernst H, Ebert S, Kuster N, Behnke W, Rittinghausen S, et al. Carcinogenicity study of GSM and DCS wireless communication signals in B6C3F1 mice. Bioelectromagnetics. 2007 Apr;28(3):173-87.
14. Bartsch H, Kupper H, Scheurlen U, Deerberg F, Seebald E, Dietz K, et al. Effect of chronic exposure to a GSM-like signal (mobile phone) on survival of female Sprague-Dawley rats: modulatory effects by month of birth and possibly stage of the solar cycle. Neuroedocrinol Lett. 2010;31(4):457-73.
15. Repacholi M, Basten A, al e. Lymphomas in El-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. Radiat Res. 1997;147:631-40.
16. Utteridge TD, Gebski V, Finnie JW, Vernon-Roberts B, Kuchel TR. Long-term exposure of E-mu-Pim1 transgenic mice to 898.4 MHz microwaves does not increase lymphoma incidence. Radiat Res. 2002 Sep;158(3):357-64.
17. Oberto G, Rolfo K, Yu P, Carbonatto M, Peano S, Kuster N, et al. Carcinogenicity study of 217 Hz pulsed 900 MHz electromagnetic fields in Pim1 transgenic mice. Radiat Res. 2007 Sep;168(3):316-26.
18. Sommer AM, Bitz AK, Streckert J, Hansen VW, Lerchl A. Lymphoma development in mice chronically exposed to UMTS-modulated radiofrequency electromagnetic fields. Radiat Res. 2007 Jul;168(1):72-80.
19. Sommer AM, Streckert J, Bitz AK, Hansen VW, Lerchl A. No effects of GSM-modulated 900 MHz electromagnetic fields on survival rate and spontaneous development of lymphoma in female AKR/J mice. BMC Cancer. 2004 Nov 11;4:77.
20. Saran A, Pazzaglia S, Mancuso M, Rebessi S, Di Majo V, Tanori M, et al. Effects of exposure of newborn patched1 heterozygous mice to GSM, 900 MHz. Radiat Res. 2007 Dec;168(6):733-40.
21. Lee HJ, Jin YB, Lee JS, Choi SY, Kim TH, Pack JK, et al. Lymphoma development of simultaneously combined exposure to two radiofrequency signals in AKR/J mice. Bioelectromagnetics. 2011;32(6):485-92.
22. Frei MR, Jauchem JR, Dusch SJ, Merritt JH, Berger RE, Stedham MA. Chronic, low-level (1.0 W/kg) exposure of mice prone to mammary cancer to 2450 MHz microwaves. Radiat Res. 1998 Nov;150(5):568-76.
23. Frei MR, Berger RE, Dusch SJ, Guel V, Jauchem JR, Merritt JH, et al. Chronic exposure of cancer-prone mice to low-level 2450 MHz radiofrequency radiation. Bioelectromagnetics. 1998;19(1):20-31.
24. Toler JC, Shelton WW, Frei MR, Merritt JH, Stedham MA. Long-term, low-level exposure of mice prone to mammary tumors to 435 MHz radiofrequency radiation. Radiat Res. 1997 Sep;148(3):227-34.

25. Jauchem JR, Ryan KL, Frei MR, Dusch SJ, Lehnert HM, Kovatch RM. Repeated exposure of C3H/HeJ mice to ultra-wideband electromagnetic pulses: lack of effects on mammary tumors. Radiat Res. 2001 Feb;155(2):369-77.

26. Shirai T, Kawabe M, Ichihara T, Fujiwara O, Taki M, Watanabe S, et al. Chronic exposure to a 1.439 GHz electromagnetic field used for cellular phones does not promote N-ethylnitrosourea induced central nervous system tumors in F344 rats. Bioelectromagnetics. 2005 Jan;26(1):59-68.

27. Zook BC, Simmens SJ. The effects of pulsed 860 MHz radiofrequency radiation on the promotion of neurogenic tumors in rats. Radiat Res. 2006 May;165(5):608-15.

28. Shirai T, Ichihara T, Wake K, Watanabe S, Yamanaka Y, Kawabe M, et al. Lack of promoting effects of chronic exposure to 1.95-GHz W-CDMA signals for IMT-2000 cellular system on development of N-ethylnitrosourea-induced central nervous system tumors in F344 rats. Bioelectromagnetics. 2007 Oct;28(7):562-72.

29. Adey WR, Byus CV, Cain CD, Higgins RJ, Jones RA, Kean CJ, et al. Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats chronically exposed to 836 MHz modulated microwaves. Radiat Res. 1999 Sep;152(3):293-302.

30. Yu D, Shen Y, Kuster N, Fu Y, Chiang H. Effects of 900 MHz GSM wireless communication signals on DMBA-induced mammary tumors in rats. Radiat Res. 2006 Feb;165(2):174-80.

31. Hruby R, Neubauer G, Kuster N, Frauscher M. Study on potential effects of "902-MHz GSM-type Wireless Communication Signals" on DMBA-induced mammary tumours in Sprague-Dawley rats. Mutat Res. 2008 Jan 8;649(1-2):34-44.

32. Bartsch H, Bartsch C, Seebald E, Deerberg F, Dietz K, Vollrath L, et al. Chronic exposure to a GSM-like signal (mobile phone) does not stimulate the development of DMBA-induced mammary tumors in rats: results of three consecutive studies. Radiat Res. 2002 Feb;157(2):183-90.

33. Anane R, Dulou PE, Taxile M, Geffard M, Crespeau FL, Veyret B. Effects of GSM-900 microwaves on DMBA-induced mammary gland tumors in female Sprague-Dawley rats. Radiat Res. 2003 Oct;160(4):492-7.

34. Imaida K, Taki M, Watanabe S, Kamimura Y, Ito T, Yamaguchi T, et al. The 1.5 GHz electromagnetic near-field used for cellular phones does not promote rat liver carcinogenesis in a medium-term liver bioassay. Jpn J Cancer Res. 1998 Oct;89(10):995-1002.

35. Imaida K, Kuzutani K, Wang J, Fujiwara O, Ogiso T, Kato K, et al. Lack of promotion of 7,12-dimethylbenz[a]anthracene-initiated mouse skin carcinogenesis by 1.5 GHz electromagnetic near fields. Carcinogenesis. 2001 Nov;22(11):1837-41.

36. Huang TQ, Lee JS, Kim TH, Pack JK, Jang JJ, Seo JS. Effect of radiofrequency radiation exposure on mouse skin tumorigenesis initiated by 7,12-dimethybenz[alpha]anthracene. Int J Radiat Biol. 2005 Dec;81(12):861-7.

37. Paulraj R, Behari J. Effects of low level microwave radiation on carcinogenesis in Swiss Albino mice. Mol Cell Biochem. 2011 Feb;348(1-2):191-7.

38. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965 May;58:295-300.

39. Repacholi MH, Lerchl A, Roosli M, Sienkiewicz Z, Auvinen A, Breckenkamp J, et al. Systematic review of wireless phone use and brain cancer and other head tumors. Bioelectromagnetics. 2012 Apr;33(3):187-206.

40. Lai H, Singh NP. Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. Int J Radiat Biol. 1996 Apr;69(4):513-21.

41. Lai H. Interaction of microwaves and a temporally incoherent magnetic field on spatial learning in the rat. Physiol Behav. 2004 Oct 15;82(5):785-9.

42. Verschaeve L, Heikkinen P, Verheyen G, Van Gorp U, Boonen F, Vander Plaetse F, et al. Investigation of co-genotoxic effects of radiofrequency electromagnetic fields in vivo. Radiat Res. 2006 May;165(5):598-607.

43. Belyaev IY, Koch CB, Terenius O, Roxstrom-Lindquist K, Malmgren LO, W HS, et al. Exposure of rat brain to 915 MHz GSM microwaves induces changes in gene expression but not double stranded DNA breaks or effects on chromatin conformation. Bioelectromagnetics. 2006 May;27(4):295-306.

44. Ferreira AR, Knakievicz T, Pasquali MA, Gelain DP, Dal-Pizzol F, Fernandez CE, et al. Ultra high frequency-electromagnetic field irradiation during pregnancy leads to an increase in erythrocytes micronuclei incidence in rat offspring. Life Sci. 2006 Dec 3;80(1):43-50.

45. Gurbuz N, Sirav B, Yuvaci HU, Turhan N, Coskun ZK, Seyhan N. Is there any possible genotoxic effect in exfoliated bladder cells of rat under the exposure of 1800 MHz GSM-like modulated Radio Frequency Radiation (RFR)? Electromagn Biol Med. 2010;29(3):98-104.

46. Oral B, Guney M, Ozguner F, Karahan N, Mungan T, Comlekci S, et al. Endometrial apoptosis induced by a 900-MHz mobile phone: preventive effects of vitamins E and C. Adv Ther. 2006 Nov-Dec;23(6):957-73.

47. Guney M, Ozguner F, Oral B, Karahan N, Mungan T. 900 MHz radiofrequency-induced histopathologic changes and oxidative stress in rat endometrium: protection by vitamins E and C. Toxicol Ind Health. 2007 Aug;23(7):411-20.

48. Dasdag S, Akdag MZ, Ulukaya E, Uzunlar AK, Ocak AR. Effect of mobile phone exposure on apoptotic glial cells and status of oxidative stress in rat brain. Electromagn Biol Med. 2009;28(4):342-54.

49. Tarantino P, Lanubile R, Lacalandra G, Abbro L, Dini L. Post-continuous whole body exposure of rabbits to 650 MHz electromagnetic fields: effects on liver, spleen, and brain. Radiat Environ Biophys. 2005 May;44(1):51-9.

50. Kim TH, Huang TQ, Jang JJ, Kim MH, Kim HJ, Lee JS, et al. Local exposure of 849 MHz and 1763 MHz radiofrequency radiation to mouse heads does not induce cell death or cell proliferation in brain. Exp Mol Med. 2008 Jun 30;40(3):294-303.

51. Poulletier de Gannes F, Lagroye I, Veyret B. Report on the analysis of risks associated to exposure to EMF: in vitro and in vivo (animals) studies. Milan, Italy: European Health Risk Assessment Network on Electromagnetic Fields Exposure; 2010 Jul.
Available from: http://efhran.polimi.it/docs/IMS-EFHRAN_09072010.pdf

52. Masuda H, Ushiyama A, Takahashi M, Wang J, Fujiwara O, Hikage T, et al. Effects of 915 MHz electromagnetic-field radiation in TEM cell on the blood-brain barrier and neurons in the rat brain. Radiat Res. 2009;172(1):66-73.

53. Finnie JW. Expression of the immediate early gene, c-fos, in mouse brain after acute global system for mobile communication microwave exposure. Pathology (Phila). 2005 Jun;37(3):231-3.

54. Finnie JW, Cai Z, Blumbergs PC, Manavis J, Kuchel TR. Stress response in mouse brain after long-term (2 year) exposure to mobile telephone radiofrequency fields using the immediate early gene, c-fos. Pathology (Phila). 2007 Apr;39(2):271-3.

55. Paparini A, Rossi P, Gianfranceschi G, Brugaletta V, Falsaperla R, De Luca P, et al. No evidence of major transcriptional changes in the brain of mice exposed to 1800 MHz GSM signal. Bioelectromagnetics. 2008 May;29(4):312-23.

56. Finnie JW, Chidlow G, Blumbergs PC, Manavis J, Cai Z. Heat shock protein induction in fetal mouse brain as a measure of stress after whole of gestation exposure to mobile telephony radiofrequency fields. Pathology (Phila). 2009;41(3):276-9.

57. Whitehead TD, Moros EG, Brownstein BH, Roti Roti JL. The number of genes changing expression after chronic exposure to code division multiple access or frequency DMA radiofrequency radiation does not exceed the false-positive rate. Proteomics. 2006 Sep;6(17):4739-44.

58. Chauhan V, Qutob SS, Lui S, Mariampillai A, Bellier PV, Yauk CL, et al. Analysis of gene expression in two human-derived cell lines exposed in vitro to a 1.9 GHz pulse-modulated radiofrequency field. Proteomics. 2007 Nov;7(21):3896-905.

59. Salford LG, Brun A, Sturesson K, Eberhardt JL, Persson BR. Permeability of the blood-brain barrier induced by 915 MHz electromagnetic radiation, continuous wave and modulated at 8, 16, 50, and 200 Hz. Microsc Res Tech. 1994 Apr 15;27(6):535-42.

60. Salford LG, Brun AE, Eberhardt JL, Malmgren L, Persson BR. Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones. Environ Health Perspect. 2003 Jun;111(7):881-3; discussion A408.

61. Nittby H, Brun A, Eberhardt J, Malmgren L, Persson BRR, Salford LG. Increased blood-brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone. Pathophysiology. 2009;16(2/3):103-12.

62. Finnie JW, Blumbergs PC, Cai Z, Manavis J, Kuchel TR. Effect of mobile telephony on blood-brain barrier permeability in the fetal mouse brain. Pathology (Phila). 2006 Feb;38(1):63-5.

63. Finnie JW, Blumbergs PC, Cai Z, Manavis J, Kuchel TR. Neonatal mouse brain exposure to mobile telephony and effect on blood-brain barrier permeability. Pathology (Phila). 2006 Jun;38(3):262-3.

64. Sirav B, Seyhan N. Blood-brain barrier disruption by continuous-wave radio frequency radiation. Electromagn Biol Med. 2009;28(2):215-22.

65. McQuade JM, Merritt JH, Miller SA, Scholin T, Cook MC, Salazar A, et al. Radiofrequency-radiation exposure does not induce detectable leakage of albumin across the blood-brain barrier. Radiat Res. 2009 May;171(5):615-21.

66. Finnie JW, Blumbergs PC, Cai Z, Manavis J. Expression of the water channel protein, aquaporin-4, in mouse brains exposed to mobile telephone radiofrequency fields. Pathology (Phila). 2009;41(5):473-5.

67. Sirav B, Seyhan N. Effects of radiofrequency radiation exposure on blood-brain barrier permeability in male and female rats. Electromagn Biol Med. 2011 Dec;30(4):253-60.

68. Stam R. Electromagnetic fields and the blood-brain barrier. Brain Res Brain Res Rev. 2010;65(1):80-97.

69. Elder JA. Radiofrequency studies on tumorigenesis and the blood-brain barrier in lab animals support the conclusion of no adverse effects without significant tissue temperature increase. Electromagnetic Compatibility (APEMC), 2010 Asia-Pacific Symposium on Computing & Processing (Hardware/Software); Fields, Waves & Electromagnetics; Signal Processing & Analysis; Apr 12-16; Beijing, China2010.
Available from:
http://ieeexplore.ieee.org/xpl/articleDetails.jsp?reload=true&arnumber=5475527&contentType=Conference+Publications

70. Brillaud E, Piotrowski A, de Seze R. Effect of an acute 900MHz GSM exposure on glia in the rat brain: a time-dependent study. Toxicology. 2007 Aug 16;238(1):23-33.

71. Ammari M, Brillaud E, Gamez C, Lecomte A, Sakly M, Abdelmelek H, et al. Effect of a chronic GSM 900 MHz exposure on glia in the rat brain. Biomed Pharmacother. 2008 Apr-May;62(4):273-81.

72. Ammari M, Gamez C, Lecomte A, Sakly M, Abdelmelek H, De Seze R. GFAP expression in the rat brain following sub-chronic exposure to a 900 MHz electromagnetic field signal. Int J Radiat Biol. 2010;86(5):367-75.

73. Yilmaz F, Dasdag S, Akdag MZ, Kilinc N. Whole-body exposure of radiation emitted from 900 MHz mobile phones does not seem to affect the levels of anti-apoptotic bcl-2 protein. Electromagn Biol Med. 2008;27(1):65-72.

74. Bas O, Odaci E, Kaplan S, Acer N, Ucok K, Colakoglu S. 900 MHz electromagnetic field exposure affects qualitative and quantitative features of hippocampal pyramidal cells in the adult female rat. Brain Res. 2009;1265:178-85.

75. Maskey D, Kim M, Aryal B, Pradhan J, Choi IY, Park KS, et al. Effect of 835 MHz radiofrequency radiation exposure on calcium binding proteins in the hippocampus of the mouse brain. Brain Res. 2010;1313:232-41.

76. Finnie JW, Cai Z, Manavis J, Helps S, Blumbergs PC. Microglial activation as a measure of stress in mouse brains exposed acutely (60 minutes) and long-term (2 years) to mobile telephone radiofrequency fields. Pathology (Phila). 2010 Feb;42(2):151-4.

77. Cobb BL, Jauchem JR, Adair ER. Radial arm maze performance of rats following repeated low level microwave radiation exposure. Bioelectromagnetics. 2004 Jan;25(1):49-57.

78. Cosquer B, Kuster N, Cassel JC. Whole-body exposure to 2.45 GHz electromagnetic fields does not alter 12-arm radial-maze with reduced access to spatial cues in rats. Behav Brain Res. 2005 Jun 20;161(2):331-4.

79. Kumlin T, Iivonen H, Miettinen P, Juvonen A, van Groen T, Puranen L, et al. Mobile phone radiation and the developing brain: behavioral and morphological effects in juvenile rats. Radiat Res. 2007 Oct;168(4):471-9.

80. Ammari M, Jacquet A, Lecomte A, Sakly M, Abdelmelek H, de Seze R. Effect of head-only sub-chronic and chronic exposure to 900-MHz GSM electromagnetic fields on spatial memory in rats. Brain Inj. 2008 Dec;22(13-14):1021-9.

81. Narayanan SN, Kumar RS, Potu BK, Nayak S, Mailankot M. Spatial memory performance of Wistar rats exposed to mobile phone. Clinics (Sao Paulo). 2009;64(3):231-4.

82. Arendash GW, Sanchez-Ramos J, Mori T, Mamcarz M, Lin X, Runfeldt M, et al. Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. J Alzheimers Dis. 2010;19(1):191-210.

83. Nasta F, Prisco MG, Pinto R, Lovisolo GA, Marino C, Pioli C. Effects of GSM-modulated radiofrequency electromagnetic fields on B-cell peripheral differentiation and antibody production. Radiat Res. 2006 Jun;165(6):664-70.

84. Prisco MG, Nasta F, Rosado MM, Lovisolo GA, Marino C, Pioli C. Effects of GSM-modulated radiofrequency electromagnetic fields on mouse bone marrow cells. Radiat Res. 2008 Dec;170(6):803-10.

85. Vinogradov GI, Dumanskii Iu D. [Changes in the antigenic properties of tissues and autoallergic processes under the influence of ultrahigh frequency energy]. Biull Eksp Biol Med. 1974 Aug;78(8):76-9.

86. Shandala MG, Vinogradov GI. Autoallergic effects of electromagnetic energy of the MW-range exposure and their influence on a foetus and posterity [Russian]. Bull Acad Med Sci USSR. 1982;10:13-6.

87. Poulletier de Gannes F, Taxile M, Duleu S, Hurtier A, Haro E, Geffard M, et al. A confirmation study of Russian and Ukrainian data on effects of 2450 MHz microwave exposure on immunological processes and teratology in rats. Radiat Res. 2009 Nov;172(5):617-24.

88. Grigoriev YG, Grigoriev OA, Ivanov AA, Lyaginskaya AM, Merkulov AV, Shagina NB, et al. Confirmation studies of Soviet research on immunological effects of microwaves: Russian immunology results. Bioelectromagnetics. 2010;31(8):589-602.

89. Repacholi M, Buschmann J, Pioli C, Sypniewska R. An international project to confirm Soviet-era results on immunological and teratological effects of RF field exposure in Wistar rats and comments on Grigoriev et al. [2010]. Bioelectromagnetics. 2011 May;32(4):325-30.

90. Grigoriev Y. Comments from the Russian group on Repacholi et al. "An international project to confirm Soviet era results on immunological and teratological effects of RF field exposure in Wistar rats and comments on Grigoriev et al. [2010]". Bioelectromagnetics. 2011 May;32(4):331-2.

91. Bakos J, Kubinyi G, Sinay H, Thuroczy G. GSM modulated radiofrequency radiation does not affect 6-sulfatoxymelatonin excretion of rats. Bioelectromagnetics. 2003 Dec;24(8):531-4.

92. Koyu A, Ozguner F, Cesur G, Gokalp O, Mollaoglu H, Caliskan S, et al. No effects of 900 MHz and 1800 MHz electromagnetic field emitted from cellular phone on nocturnal serum melatonin levels in rats. Toxicol Ind Health. 2005 Mar;21(1-2):27-31.

93. Hata K, Yamaguchi H, Tsurita G, Watanabe S, Wake K, Taki M, et al. Short term exposure to 1439 MHz pulsed TDMA field does not alter melatonin synthesis in rats. Bioelectromagnetics. 2005 Jan;26(1):49-53.

94. Lerchl A, KrÃ¼ger H, Niehaus M, Streckert JR, Bitz AK, Hansen V. Effects of mobile phone electromagnetic fields at nonthermal SAR values on melatonin and body weight of Djungarian hamsters (Phodopus sungorus). J Pineal Res. 2008;44(3):267-72.

95. Lee HJ, Lee JS, Pack JK, Choi HD, Kim N, Kim SH, et al. Lack of teratogenicity after combined exposure of pregnant mice to CDMA and WCDMA radiofrequency electromagnetic fields. Radiat Res. 2009 Nov;172(5):648-52.

96. Ogawa K, Nabae K, Wang J, Wake K, Watanabe S, Kawabe M, et al. Effects of gestational exposure to 1.95-GHz W-CDMA signals for IMT-2000 cellular phones: Lack of embryotoxicity and teratogenicity in rats. Bioelectromagnetics. 2009;30(3):205-12.

97. Sommer AM, Grote K, Reinhardt T, Streckert J, Hansen V, Lerchl A. Effects of radiofrequency electromagnetic fields (UMTS) on reproduction and development of mice: a multi-generation study. Radiat Res. 2009 Jan;171(1):89-95.

98. Takahashi S, Imai N, Nabae K, Wake K, Kawai H, Wang J, et al. Lack of adverse effects of whole-body exposure to a mobile telecommunication electromagnetic field on the rat fetus. Radiat Res. 2010;173(3):362-72.

99. Sambucci M, Laudisi F, Nasta F, Pinto R, Lodato R, Altavista P, et al. Prenatal exposure to non-ionizing radiation: effects of WiFi signals on pregnancy outcome, peripheral B-cell compartment and antibody production. Radiat Res. 2010 Dec;174(6):732-40.

100. Fragopoulou AF, Koussoulakos SL, Margaritis LH. Cranial and postcranial skeletal variations induced in mouse embryos by mobile phone radiation. Pathophysiology. 2010 Jun;17(3):169-77.

101. Gul A, Celebi H, Ugras S. The effects of microwave emitted by cellular phones on ovarian follicles in rats. Arch Gynecol Obstet. 2009 Nov;280(5):729-33.

102. Watilliaux A, Edeline JM, Lévêque P, Jay TM, Mallat M. Effect of exposure to 1,800 MHz electromagnetic fields on heat shock proteins and glial cells in the brain of developing rats. Neurotox Res. 2011;20(2):109-19.

103. Tomruk A, Guler G, Dincel AS. The influence of 1800 MHz GSM-like signals on hepatic oxidative DNA and lipid damage in nonpregnant, pregnant, and newly born rabbits. Cell Biochem Biophys. 2010;56(1):39-47.

104. Adang D, Remacle C, Vander Vorst A. Results of a long-term low-level microwave exposure of rats. IEEE Trans Microw Theory Tech. 2009;57:2488-97.

105. Marino C, Lagroye I, Scarfi MR, Sienkiewicz Z. Are the young more sensitive than adults to the effects of radiofrequency fields? An examination of relevant data from cellular and animal studies. Prog Biophys Mol Biol. 2011 Sep 8.